

Advances in

HETEROCYCLIC CHEMISTRY

Edited by

ALAN R. KATRITZKY, FRS

Kenan Professor of Chemistry

Department of Chemistry

University of Florida

Gainesville, Florida

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Contributors

Numbers in parentheses indicate the pages on which the authors' contributions begin.

Paul W. Groundwater (89), School of Health Sciences, University of Sunderland, Sunderland SR1 3SD, United Kingdom

István Hermecz (1), Chinoin Pharmaceutical and Chemical Works, Ltd., Research Center, 1325 Budapest, Hungary

Munawar Ali Munawar (89), Department of Chemistry, Islamia University, Bawalpur, Pakistan

Mohammed A. E. Shaban (163), Department of Chemistry, Faculty of Science, Alexandria University, Alexandria 21321, Egypt

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Preface

Volume 70 of *Advances in Heterocyclic Chemistry* consists of three chapters together with the Subject Index for Volumes 61 through 70. The first contribution by Dr. István Hermecz (Chinoin, Hungary) continues with Part II of his set of three chapters on condensed pyridines. Part I, in Volume 69, covered pyrido[1,2-*b*][1,2]oxazines, -thiazines, and -pyridazines, and the present chapter deals with [1,2-*c*]-fused 1,3-oxanes, 1,2-thiazines, and -pyrimidines. The third part will appear in a subsequent volume of our series and will deal with 1,4-oxazines and 1,4-thiazines, fused pyridine rings.

The second chapter by Dr. P. W. Groundwater (University of Sunderland, UK) and Dr. M. A. Munawar (Islamia University, Pakistan) is an overview of heterocycle-fused acridines, classes of compounds which have not previously been reviewed and which show a variety of biological activities.

Volume 70 also contains the second and final installment of the chemistry of *C*-nucleosides and their analogs by Professor M. A. E. Shaban of Alexandria University, Egypt. Previously, in Volume 68, Professor Shaban covered *C*-nucleosides of heteromonocyclic bases. The present chapter deals with the *C*-nucleosides of condensed heterocyclic bases and thus completes the first comprehensive review of *C*-nucleosides.

As an Index Volume, Volume 70 of *Advances in Heterocyclic Chemistry* contains an update of the general Subject Index (in addition to the comprehensive indexes of authors and of titles, which appear in each volume of *Advances in Heterocyclic Chemistry*). Volume 70 contains Subject Index entries for Volumes 61 to 70 and thus continues the Subject Index, which was covered previously in Volume 40 for Volumes 1–40, in Volume 45 for Volumes 41–45, in Volume 53 for Volumes 46–53, and in Volume 60 for Volumes 55–60. Volume 54, as a monograph volume, contained its own subject index.

ALAN R. KATRITZKY

Chemistry of Pyrido[1,2-*c*][1,3]oxazines, Pyrido[1,2-*c*][1,3]thiazines, Pyrido[1,2-*c*]pyrimidines, and Their Benzologs: Part II

ISTVÁN HERMECZ

*Chinoin Pharmaceutical and Chemical Works, Ltd., Research
Center, 1325 Budapest, Hungary*

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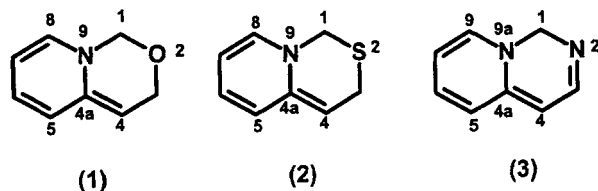
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I. Introduction

The chemistry of the pyrido[1,2-*c*][1,3]oxazines (**1**), pyrido[1,2-*c*][1,3]thiazines (**2**), and pyrido[1,2-*c*]pyrimidines (**3**) (Scheme 1) and their benzologs (**4**)–(**17**) (Schemes 2–4) has not been systematically reviewed. Only Mosby's review in 1961 treated the early articles on pyrido[1,2-*c*][1,3]oxazines [61HC(15-2)1201], pyrido[1,2-*c*]pyrimidines [61HC(15-2)1203], and pyrimido[6,1-*a*]isoquinolines [61HC(15-2)1207], and a review in 1986 dealt with pyrido[1,2-*c*]quinazolines [86AHC(39)281].

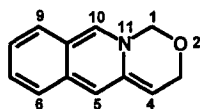
In the present article the primary chemical literature up to the end of 1996 has been surveyed. *Chemical Abstracts* Subject and Chemical Substance indexes up to and including Volume 124 have been searched.

Perhydropyrido[1,2-*c*][1,3]oxazines, pyrido[1,2-*c*][1,3]oxazines, [1,3]oxazino[3,4-*a*]quinolines, and perhydropyrido[1,2-*c*]pyrimidines are applied as key intermediates in the total syntheses of different alkaloids. Other examples of these ring systems have aroused much interest owing to their valuable pharmacological properties. Of these actisomide (**18**) and trequinsen (**19**) were introduced into human therapy as antiarrhythmic and antihypertensive agents, respectively.



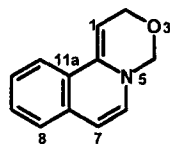
SCHEME 1

Benzo Derivatives of Pyrido[1,2-c][1,3]oxazine



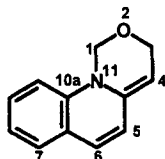
(4)

1*H*,3*H*-[1,3]Oxazino[3,4-*b*]isoquinoline



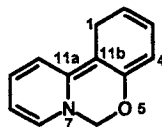
(5)

2*H*,4*H*-[1,3]Oxazino[4,3-*a*]isoquinoline



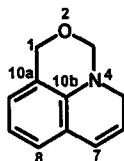
(6)

1*H*,3*H*-[1,3]Oxazino[3,4-*a*]quinoline



(7)

1*H*,6*H*-Pyrido[1,2-*c*][1,3]benzoxazine

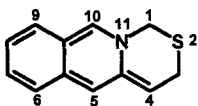


(8)

1*H*,3*H*,5*H*-Pyrido[3,2,1-*ij*][3,1]benzoxazine

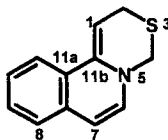
SCHEME 2

Benzo Derivatives of Pyrido[1,2-c][1,3]thiazine



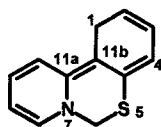
(9)

1*H*,3*H*-[1,3]Thiazino[3,4-*b*]isoquinoline



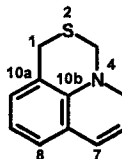
(10)

2*H*,4*H*-[1,3]Thiazino[4,3-*a*]isoquinoline



(11)

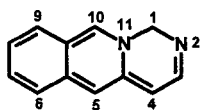
1*H*,6*H*-Pyrido[1,2-*c*][1,3]benzothiazine



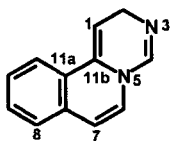
(12)

1*H*,3*H*,5*H*-Pyrido[3,2,1-*ij*][3,1]benzothiazine

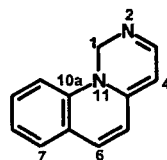
SCHEME 3

Benzo Derivatives of Pyrido[1,2-*c*]pyrimidine

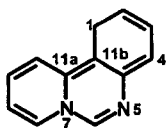
(13)



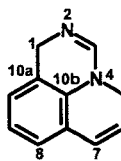
(14)



(15)

1*H*-Pyrimido[1,6-*b*]isoquinoline2*H*-Pyrimido[6,1-*a*]isoquinoline1*H*-Pyrimido[1,6-*a*]quinoline

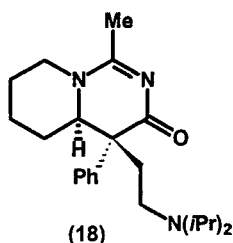
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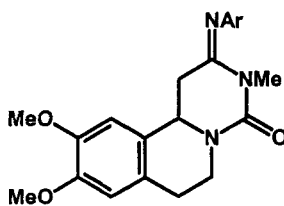
(17)

1*H*-Pyrido[1,2-*c*]quinazoline1*H*,5*H*-Pyrido[3,2,1-*ij*]quinazoline

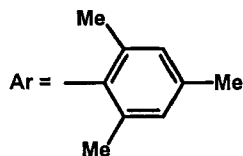
SCHEME 4



(18)



(19)



In the following sections, the physicochemical and spectroscopic properties, reactions, syntheses, and, more briefly, the use of these ring systems are discussed. Within the individual sections the pyrido[1,2-*c*][1,3]oxazines and their benzologs, pyrido[1,2-*c*][1,3]thiazines and their benzologs, and pyrido[1,2-*c*]pyrimidines and their benzologs are dealt with.

II. Structure

A. PYRIDO[1,2-*c*][1,3]OXAZINES AND THEIR BENZO DERIVATIVES

1. Thermodynamic Aspects¹

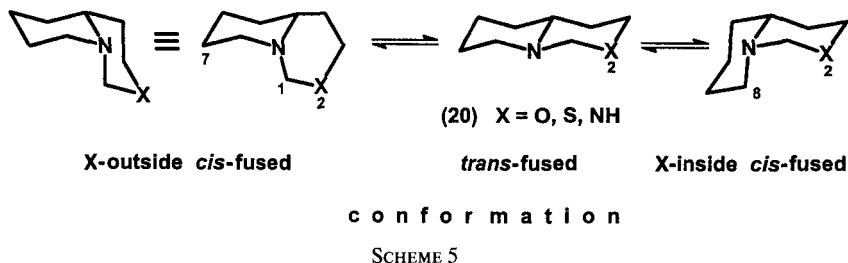
Enantiomers of 11,11*a*-dihydro-6*H*,10*H*-pyrido[1,2-*c*][1,3]benzoxazin-6-one were quantitatively separated by chiral high-performance liquid chromatography (HPLC). The first eluted enantiomer had the *R* configuration (91ACS716).

The protonation constants of *r*-4*a*,*c*-5*a*,*t*-9*a*-H and *r*-4*a*,*t*-5*a*,*c*-9*a*-H-perhydro[1,3]oxazino[3,4-*b*]isoquinolines were determined in to be 6.2 and 5.6, respectively (80HCA1158).

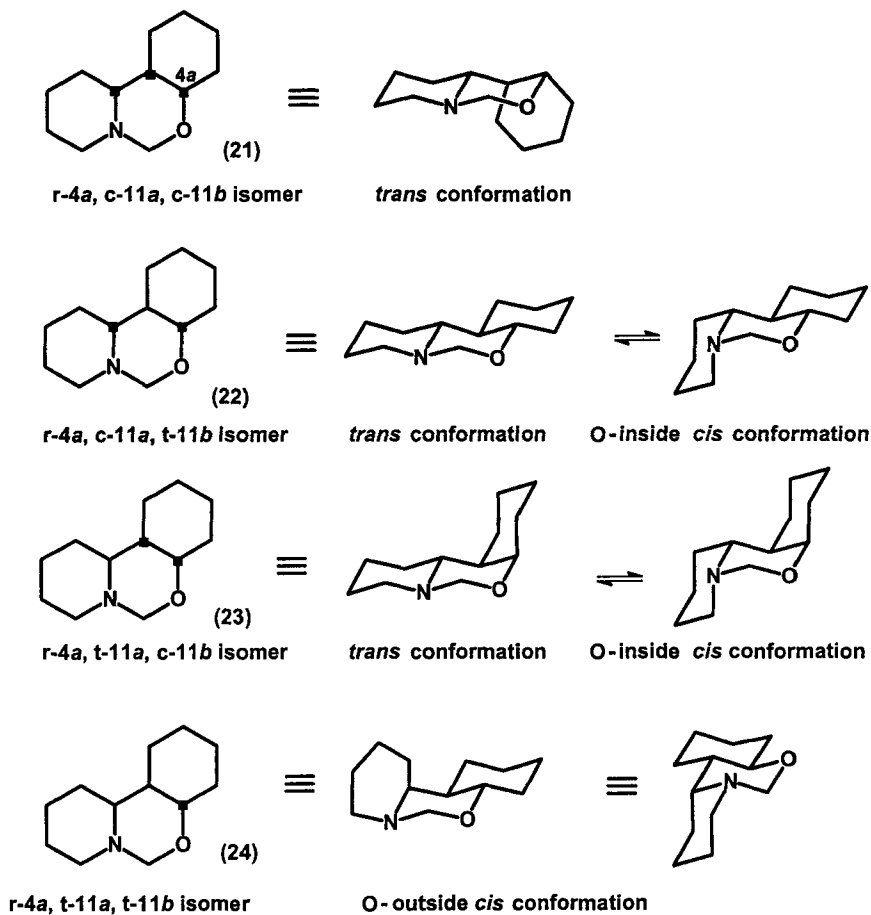
2. Theoretical Calculations

A conformational study of perhydropyrido[1,2-*c*][1,3]oxazine (**20**, X = O) and its derivatives by means of modified MM2 calculations suggested that the O-*outside cis* conformation (ca. 5.28 kcal mol⁻¹) and the *trans* conformation (ca. 1.63 kcal mol⁻¹) are less stable than the O-*inside cis* conformation (Scheme 5) [91JST(245)53]. This conclusion contradicts the experimental finding [80JCS(P2)1778] and is attributed to underestimation of the nonbonding interaction between the C(8) methylene group and the oxygen atom or to overestimation of the anomeric effect.

Conformational analysis of perhydropyrido[1,2-*c*][1,3]benzoxazines (**21–24**) (Scheme 6) by a modification of the MM285 force field predicts that the *trans* conformation of the heterocycles is the most stable for the *r*-



¹ In a saturated ring system, the stereochemistry of the hydrogens on tertiary carbon atoms is indicated by *r*, *c*, and *t* symbols (e.g., *r*-4*a*, *c*-5*a*, *t*-9*a*, -H), where *r*, *c*, and *t* denote that in relation to the indicated hydrogen *r* the other hydrogens are on the same side of the ring (*cis*) or the opposite side (*trans*).



SCHEME 6

4a,c-11a,c-11b diastereomer **(21)** [92JST(274)259], as is the O-*outside cis* conformation of the heterocycles for the r-4a,t-11a,t-11b isomer **(24)**, which is consistent with qualitative experimental estimates (70T1217). It was calculated that for **21** the *trans* conformation is ca. 3.7 kcal mol⁻¹ more stable than the O-*outside cis* conformation. For the r-4a,c-11a,t-11b isomer **(22)** and the r-4a,t-11a,c-11b isomer **(23)**, it was predicted that the O-*inside cis* conformations are ca. 1.7 kcal mol⁻¹ and 1.4 kcal mol⁻¹, respectively, more stable than the respective *trans* conformations, which is the opposite of the experimentally estimated orders (70T1217).

The lack of correlation between cyclization stereoselectivity and the steric energy of the products (calculated by the MMX force field)

indicated that *cis*-7*a*,10*b*-H epimers of 1-phenyl- and 1-phenyl-7*a*-methyl-5,6,7,7*a*,8,9,10,10*b*-octahydro-3*H*-pyrido[3,2,1-*ij*][3,1]benzoxazines are formed under kinetic control from 1-(*tert*-butoxycarbonyl)-2-methoxy-3-(4-phenyl-3-butynyl)piperidines (90JOC1447).

3. Ultraviolet and Circular Dichroism Spectroscopy

No systematic ultraviolet (UV) study has been published on pyrido[1,2-*c*][1,3]oxazines and their benzo derivatives.

The optical rotatory dispersion (ORD) curves of the diastereomers of 1-(*p*-nitrophenyl)-3-methylperhydropyrido[1,2-*c*][1,3]oxazines, obtained from (–)-2-(2-hydroxypropyl)piperidine with *p*-nitrobenzaldehyde, are nearly mirror images of each other (68CJC1105). The absolute configurations in cyclohexane of the dextrorotatory *cis*-3,4*a*-H-3-phenyl- and *trans*-3,4*a*-H-3-phenylhydropyrido[1,2-*c*][1,3]oxazin-6-ones, containing 3*S*,4*a**R* and 3*S*,4*a**S* atoms, respectively, were determined on the basis of the presence of positive Cotton effects (85T2891).

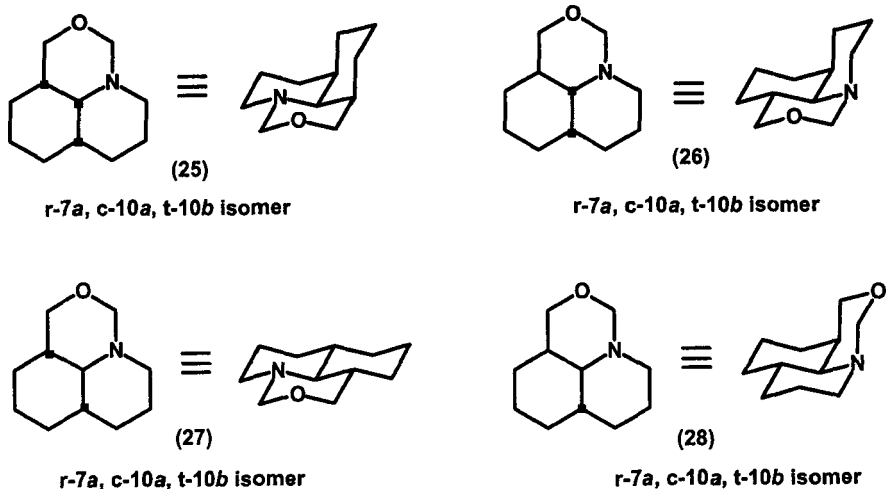
Ultraviolet and circular dichroism (CD) spectra of the epimers of 11,11*a*-dihydro-6*H*,10*H*-pyrido[1,2-*c*][1,3]benzoxazin-6-one were measured in ethanol. From the geometry obtained through empirical force-field calculations, the rotational strengths of the strong transitions in the CD spectra were calculated by the complete neglect of differential overlap (CNDO)/S method and the absolute configurations were assigned (91ACS716). The UV spectra appear as superpositions of those of *N*-vinylcarbamate and the phenyl chromophores.

4. Dipole Moment Investigations

Dipole moments of perhydropyrido[1,2-*c*][1,3]oxazine (**20**, X = O) and its four alkyl derivatives were calculated from measurements in benzene at 25°C and were used to estimate the conformational preferences of several perhydropyrido[1,2-*c*][1,3]oxazines [76JCS(P2)418]. The *trans*-fused and O-outside *cis*-fused conformers possess identical dipole moments (2.08 D), whereas that of the O-inside *cis*-fused conformers is 1.30 D.

5. Infrared Spectroscopy

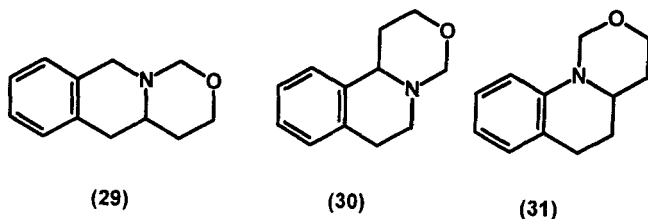
The appearance of the Bohlmann band in the infrared (IR) spectrum is frequently used to identify the *trans*-fused conformation of perhydropyrido[1,2-*c*][1,3]oxazines [66MI2; 68T4423; 70T1217, 70T3941; 71T2055; 71TL3361; 76OMR(8)258; 85T2891; 87T935] and their benzo derivatives (e.g., **21–23**, **25**, **27**, **29** [70T1217; 71TL3361; 77JCS(P2)370; 80JCS(P2)1778; 84OMR(22)424]. *cis*-Fused conformers are not expected to produce Bohl-



SCHEME 7

mann bands, since they do not allow two C—H bonds adjacent to the N to be *trans*-axial to the N lone pair of electrons. The weak Bohlmann bands in the IR spectra suggested a *cis*-fused conformation of the *r-4a, t-11a, t-11b-H* isomer of perhydropyrido[1,2-*c*][1,3]benzoxazine (**24**) (70T1217) (Scheme 6), for perhydro[3,2,1-*ij*][3,1]oxazines (**26** and **28**) (Scheme 7) [80JCS(P2)1778; 84OMR(22)424], and for hexahydro[1,3]oxazino[4,3-*a*]isoquinoline (**30**) [71TL3361; 77JCS(P2)370].

The Bohlmann bands are not suitable for recognition of a *trans*-fused conformer of hexahydro[1,3]oxazine[3,4-*a*]quinoline (**31**) and its derivatives because of the flattening of the bridgehead N pyramid, as a consequence of (*p-p*) π conjugation of the lone pair of the N atom and the aromatic π -orbitals of the benzene moiety (71TL3361).



6. ¹H NMR Spectroscopy

a. *Fully Saturated Ring Systems.* In the investigation of the conformation of perhydropyrido[1,2-*c*][1,3]oxazine (**20**, X = O), three all-chair conformations (O-outside *cis*-fused or *trans*-fused and O-inside *cis*-fused forms)

can be considered the most stable (Scheme 5). Conformers containing at least one of the rings in a boat or twisted conformation are of high energy and can be neglected. The *cis* conformers should be higher in energy than the *trans* conformer because of the presence of three *gauche*-butane interactions, which are absent in the *trans* form. At the same time, the O-inside *cis* conformation has a lower energy than the O-outside *cis* conformation, since the interaction between O(2) and the 8-methylene group is appreciably lower in the former than the interaction between the 1- and 7-methylene groups in the latter. Furthermore, in the *trans*-fused and O-outside *cis*-fused conformations, there is a destabilizing dipole-dipole interaction between the heteroatoms, which is relieved in the O-inside *cis*-fused conformation. The O-inside *cis*-fused conformation may also be stabilized by an $n_N \rightarrow \delta^*_{C-O}$ anomeric effect.

J_{gem} for the N—CH₂—O protons depends on the degree of overlap between the molecular orbitals of the methylene group and the lone pair of electrons on the adjacent N atom (68T4423). The *trans*-fused and O-outside *cis*-fused conformations, containing one of the C—H bonds of the N—CH₂—O group and the lone pair of electrons on the N atom in the *trans*-axial arrangement (A), have a more positive (smaller absolute value) J_{gem} for the N—CH₂—O group because of the more efficient overlapping between the N—CH₂—O group and the N lone pair of electrons than that of the O-inside *cis*-fused conformation containing arrangement B, where the N lone pair bisects the C(1) methylene group (Fig. 1).

J_{gem} for the C(1) methylene group is used to estimate the ratio of the *trans* and O-inside conformers of different perhydropyrido[1,2-*c*][1,3]oxazines. The expected J_{gem} is ca. -7.7 Hz in arrangement A and ca. -11 Hz in arrangement B. The measured J_{gem} of -8.0 Hz reflects a roughly 10:90 mixture of the O-inside *cis* and *trans* conformers in a 10% solution of perhydropyrido[1,2-*c*][1,3]oxazine in CCl₄ [68T4423; 80JCS(P2)1778]. The contribution of the O-outside *cis* conformer to the equilibrium was estimated to be only ca. 1% [76JCS(P2)418].

The chemical shift difference between the N—CH₂—O protons is sometimes a useful tool for prediction of the predominant conformations. $\Delta_{ax,eq}$ is around 0.5–0.9 ppm for the *trans* conformation, while a $\Delta_{ax,eq}$ value of 0.0–0.2 ppm points to the presence of the O-inside *cis* conformation.

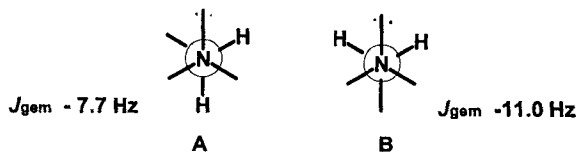
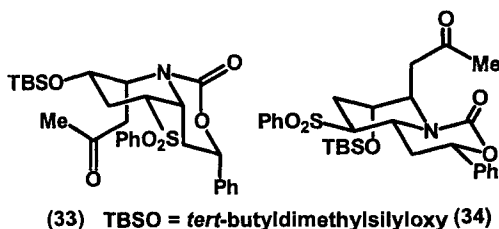
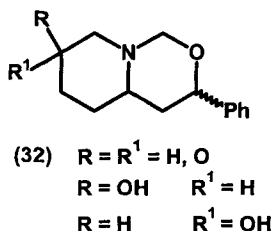


FIG. 1

A *trans* conformer, as the major conformer, was identified for 1-, 3-, or 4-substituted perhydropyrido[1,2-*c*][1,3]oxazine, independently of whether the substituent occupies an axial or an equatorial position [68T4423; 70T1217; 71TL3361; 76OMR(8)258; 92MRC129]. Whereas the *cis*-4*a*,8-H-8-methyl derivative exists in a *trans* conformation containing the methyl group in the equatorial position (68T4423; 70T1217), the *trans*-4*a*,8-H-8-methyl derivative exists as an equilibrium mixture of the *trans* conformer with an axial methyl group and the O-inside *cis* form with an equatorial methyl group (68T4423). The *cis*-4*a*,5-H-5-methyl derivative also exists as a mixture of the *trans* conformer with an axial methyl group and the O-inside *cis*-form with an equatorial methyl group (70T3941). The *cis*- and *trans*-3,4*a*-H-1-aryl-3-methylperhydropyrido[1,2-*c*][1,3]oxazines adopt *trans*-fused conformations with an equatorial aryl group (65RTC1367). The *r*-4*a*,*t*-1,*c*-8-H-1,8-dimethylperhydropyrido[1,2-*c*][1,3]oxazine exists in *trans*-fused conformation with an axial 1-methyl and an equatorial 8-methyl group (68T4423).

The *cis*-4*a*,7-H-7-ethyl derivative exists as a 3:7 mixture of the *trans* conformer with an axial ethyl group and the O-inside *cis* conformer with an equatorial ethyl group at -90°C , and as a 47:53 mixture of the *trans* and *cis* conformers at 20°C in a mixture of CDCl_3 - CFCl_3 [76JCS(P2)418]. As concerns the other epimer, the *trans* conformer is the more favored.

The values of the geminal coupling constant between the C(1) protons indicated that 5,5-dimethoxy- and 7,7-dimethoxy-3-phenylperhydro[1,2-*c*][1,3]oxazines exist predominantly in *cis*-fused ($J_{\text{gem}} \approx -10.5$ Hz) and *trans*-fused ($J_{\text{gem}} \approx -8.5$ Hz) conformations, respectively, both containing the phenyl group in the axial position (87T935). Conformational analysis of the epimers of 3-phenylperhydropyrido[1,2-*c*][1,3]oxazines (**32**) was also performed by ^1H NMR spectroscopy (85T2891).



The solvent effect on the C(1) methylene parameters in the ^1H NMR spectra of perhydropyrido[1,2-*c*][1,3]oxazine (**20**, $\text{X} = \text{O}$), its *cis*-4*a*,5-H-5-methyl derivative and **25** was investigated in six solvents [80OMR(13)159]. The positions of the equilibria were not affected significantly by solvent changes.

TABLE I
EQUILIBRIUM OF CONFORMERS OF PERHYDROPYRIDO[1,2-*c*][1,3]OXAZINE
(**20**, X = O) (88MRC748)

Conformation	Equilibrium in free base in CDCl ₃ (%)	Thermodynamically controlled protonation in D ₂ O–DCl (%)	Partially kinetically controlled protonation ^a (20 , X = O) · HCl salt in CDCl ₃ (%)
<i>trans</i>	90	93	75
O-inside <i>cis</i>	10	7	25

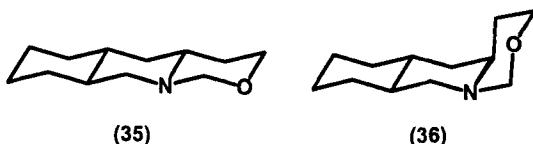
^a Prepared in sodium-dried diethyl ether with dry hydrogen chloride.

The equilibrium between the *trans* and O-inside *cis* conformers of perhydropyrido[1,2-*c*][1,3]oxazine (**20**, X = O) was frozen by protonation and deuteration (88MRC748). The ratio of the *trans* and O-inside *cis* forms was investigated by ¹H and ¹³C spectra and is tabulated in Table I. ¹H NMR spectra of the hydrochloride salt of *cis*-4*a*,8-H-8-methyl- and *trans*-4*a*,7-H-7-ethylperhydropyrido[1,2-*a*][1,3]oxazines show that these derivatives exist in a *trans*-fused conformation in CDCl₃, whereas the hydrochloride salt of the *cis*-4*a*,7-H-7-ethyl derivative is exclusively in an O-inside *cis* conformation (88MRC748).

Perhydropyrido[1,2-*c*][1,3]oxazine (**20**, X = O) exists as a 98:2 mixture of the *trans* and O-inside *cis* conformers ($\Delta G_{203} = 6.3 \text{ kJ mol}^{-1}$) at 203 K in CD₂Cl₂–CFCl₃, and as the *trans*-4*a*,4*a*-H-4-methyl derivative ($\Delta G_{193} = 5.4 \text{ kJ mol}^{-1}$) at 193 K, whereas the C(4) epimer adopts exclusively the *trans*-fused conformation at 193 K (92MRC129).

Conformational analysis of diastereomeric pyrido[1,2-*c*][1,3]oxazin-1-ones (**33** and **34**) revealed that **33** adopted an O-inside *cis*-fused conformation, whereas **34** existed in a *trans*-fused form (96SL100). Both isomers contained the C(8) substituent in an axial position to avoid an A^(1,3) strain.

Both the geminal coupling constant and the chemical shift difference of the 1-methylene group are indicative of the predominance of the *trans*-fused conformation for (+)-*cis*-4*a*,5*a*-H-perhydro[1,3]oxazino[3,4-*b*]isoquinoline (**35**) [$\Delta_{\text{ax,eq}} \approx 0.87 \text{ ppm}$ and $J_{\text{gem}} = -8.5 \text{ Hz}$] and of the predominance of the O-inside *cis*-fused conformation for (–)-*cis*-4*a*,9*a*-H-perhydro[1,3]oxazino[3,4-*b*]isoquinoline (**36**) ($\Delta_{\text{ax,eq}} \approx 0.0 \text{ ppm}$ and $J_{\text{gem}} = -10 \text{ Hz}$) (80HCA1158).



Conformation analysis of isomeric perhydropyrido[1,2-*c*][1,3]benzoxazines (**21–24**) by means of ^1H NMR studies demonstrates that the predominant conformers of the isomers **21**, **22**, and **23** contain a *trans*-fused pyrido[1,2-*c*][1,3]oxazine moiety, whereas that of **24** has an O-outside *cis*-fused pyrido[1,2-*c*][1,3]oxazine moiety (see Scheme 6) (70T1217; 71TL3361).

Stereochemically locked all-chair conformations of perhydropyrido[3,2,1-*ij*][3,1]benzoxazines (**25–28**) are useful models for the investigation of the conformational equilibria of the mobile perhydropyrido[1,2-*c*][1,3]oxazine and its derivatives (see Table II) [80JCS(P2)1778]. In the stereoisomers **25** and **27**, *trans*-fused heterocycles are indicated by the $J_{3\text{ax},3\text{eq}}$ values of -7.67 and -7.55 Hz, and the large $\Delta_{3\text{ax},3\text{eq}}$ values of 0.87 and 0.84 ppm, respectively, while the $J_{3\text{ax},3\text{eq}}$ value of -10.8 Hz for **26** and the $\Delta_{3\text{ax},3\text{eq}}$ and $\Delta_{5\text{ax},5\text{eq}}$ values of 0.40 and 0.27 ppm for **28** indicate the O-inside *cis*-fused and O-outside *cis*-fused conformations, respectively (see Scheme 7).

The ^1H NMR spectra of **25** were recorded in six solvents. $J_{3\text{ax},3\text{eq}}$ and $\Delta_{3\text{ax},3\text{eq}}$ were found to vary with the solvent, which is attributed to solvation effects [80OMR(13)159]. The stereochemistry of the two 5-methyl epimers of **26** and **27** and of the equatorially oriented methyl derivatives of **25** and **28** was investigated by ^1H NMR spectroscopy [84OMR(22)424].

b. *Partly Saturated Ring Systems.* The insertion of a 6,7 or 7,8 double bond in perhydropyrido[1,2-*c*][1,3]oxazine (**20**, $\text{X} = \text{O}$) [e.g., hexahydro[1,3]oxazino[3,4-*b*]isoquinoline (**29**) ($J_{\text{C}(1)\text{H}2} = -8.2$ Hz, $\Delta_{1\text{eq}1\text{ax}} = 0.9$ ppm in C_6D_6) and hexahydro[1,3]oxazino[3,4-*a*]quinoline (**31**) ($J_{\text{C}(1)\text{H}2} = -10.5$ Hz, $\Delta_{1\text{eq}1\text{ax}} = 1.21$ ppm in C_6D_6)] does not affect the position of the conformational equilibrium of the preferred *trans*-fused conformer. However, the insertion of a 5,6 double bond [hexahydro[1,3]oxazino[4,3-*a*]isoquinoline (**30**) ($J_{\text{C}(1)\text{H}2} = -10.2$ Hz, $\Delta_{4\text{eq}4\text{ax}} = 0.20$ ppm in C_6D_6)] moves the position of the conformational equilibrium towards the O-inside *cis*-fused conformer

TABLE II
SOME ^1H NMR DATA ON STEREOCHEMICALLY LOCKED PERHYDROPYRIDO[3,2,1-*ij*][1,3]BENZOXAZINES (**25–28**) IN CDCl_3 AT 270 MHz [80JCS(P2)1778]

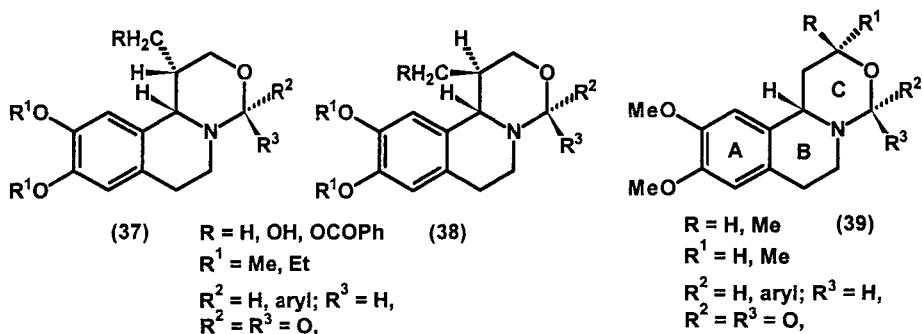
	N-CH _{eq} -O N-CH _{eq} H _{ax} -O	N-CH _{ax} -O N-CH _{eq} H _{ax} -O	$\Delta_{\text{aq,ex}}$	$^3J_{\text{NCH}_2\text{O}}$ (Hz)
25	4.27	3.40	0.87	-7.67
26	4.56	4.44	0.12	-10.8
27	4.35	3.51	0.84	-7.55
28	4.55	4.15	0.40	-7.55

[71TL3361; 77JCS(P2)370]. In the latter case, the *trans*-fused conformer would involve a ring fusion strain that is missing in the alternative O-inside *cis*-fused conformer [77JCS(P2)370]. The rather negative coupling constant for the C(1)methylene (-10.5 Hz) in **31** is a consequence of the interaction of the N lone pair with the aromatic ring, which reduces the lone pair C(1)-methylene overlap [71TL3361].

Hexahydro[1,3]oxazino[3,4-*a*]quinoline (**31**) and its *cis*-3,4*a*-H-3-methyl and *trans*-3,4*a*-H-3-methyl derivatives exist predominantly in *trans*-fused conformations [77JCS(P2)1592].

cis-4,11*b*-H-4-Aryl-1,2,4,6,7,11*b*-hexahydro[1,3]oxazino[4,3-*a*]isoquinoline in solution adopts the O-inside *cis* conformation with an equatorial aryl group at position 4 [76OMR(8)258].

The presence of a substituent at position 1 influences the ring junction in 1,2,4,6,7,11*b*-hexahydro[1,3]oxazino[4,3-*a*]isoquinolines (**37** and **38**, $R^2 = \text{H, aryl}$; $R^3 = \text{H}$) (90CB803; 92T4937). *trans*-1,11*b*-H-1,2,4,6,7,11*b*-Hexahydro[1,3]oxazino[4,3-*a*]isoquinolines (**37**, $R^2 = \text{H, aryl}$; $R^3 = \text{H}$) preferentially exist in the O-inside *cis*-fused conformation containing the substituent CH_2R in the equatorial position, but *cis*-1,11*b*-H-1,2,4,6,7,11*b*-hexahydro-[1,3]oxazino[4,3-*a*]isoquinolines (**38**, $R^2 = \text{H, aryl}$; $R^3 = \text{H}$) adopt a *trans*-fused conformation with an axial substituent CH_2R (90CB803; 92T4937).

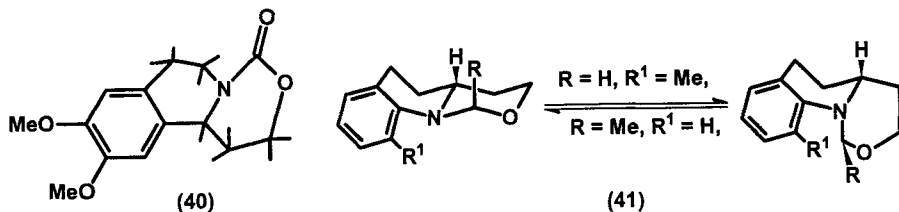


An analysis of ^1H and ^{13}C NMR data led to the conclusion that both epimers of 2-methyl-1,2,4,6,7,11*b*-hexahydro[1,3]oxazino[4,3-*a*]isoquinolines (**39**, $R^2 = \text{H, aryl}$; $R^3 = \text{H}$) are present in a *trans*-fused B/C conformation (92T4937).

4-Aryl derivatives of **37** and **38** ($R^2 = \text{aryl}$; $R^3 = \text{H}$) contain the 4-aryl group in the equatorial position (90CB803; 92T4937). 4-Oxo derivatives **37**, **38**, and **39** ($R^2 = R^3 = \text{O}$) adopt the conformation of **40** (92T4937).

Whereas 1,3,4,4*a*,5,6-hexahydro[1,3]oxazino[3,4-*a*]quinoline (**41**, $R = R^1 = \text{H}$) and its 1-, 3-, and 4-methyl derivatives adopt *trans* conformations [71TL3361; 77JCS(P2)1592; 93JCR(S)170], its 10-methyl derivative (**41**,

R = H, R¹ = Me) exists predominantly in the O-outside *cis*-fused conformation, because of nonbonded interactions between the methyl substituent and C(1)–H_{eq} in the other conformations [93JCR(S)170]. The *trans*-1,4a-H-1-methyl derivative (**41**, R = Me, R¹ = H) contains the methyl group in the axial position in the predominant *trans*-fused conformation [93JCR(S)170].



The stereochemistry of the two 5-methyl epimers of **26** and **27** and of the equatorially oriented methyl derivatives of **25** and **28** was investigated by ¹H NMR spectroscopy [84OMR(22)424].

7. ¹³C NMR Spectroscopy

Low-temperature ¹³C NMR spectroscopy indicated that perhydropyrido[1,2-*c*][1,3]oxazine at equilibrium at 203 K in CD₂Cl₂–CFCl₃ solution adopts a 98:2 ratio of *trans* and O-inside *cis* conformers ($\Delta G^\circ_{203} = 6.3$ kJ mol⁻¹) (92MRC129). A similar equilibrium (ca. 96.5:3.5; $\Delta G^\circ_{193} = 5.4$ kJ mol⁻¹) is adopted by the *trans*-4,4a-H-4-methyl derivative, whereas the C(4) epimer adopts exclusively the *trans* conformation. The ¹³C NMR spectrum of the hydrochloride salt of perhydropyrido[1,2-*c*][1,3]oxazine has also been recorded in CDCl₃ (88MRC748) (see Table III).

¹³C NMR data on the C(3) epimers of 3-phenylperhydropyrido[1,2-*c*][1,3]oxazines (**32**) were used for the determination of their stereostructures (85T2891). ¹³C NMR data have also been published on perhydro[1,3]oxazino[3,4-*b*]isoquinolines (**35** and **36**) (80HCA1158).

The ¹³C NMR data of isomeric perhydropyrido[1,2-*c*][1,3]benzoxazines (**21**–**24**) (93MRC505) are consonant with the predominant conformations (see Scheme 6) previously assigned on the basis of the ¹H NMR data (70T1217). The ¹³C NMR spectra of perhydro[3,2,1-*ij*][1,3]benzoxazines (**25**–**28**) (Scheme 7) (Table III) (92MRC129), and 2,3,4,4a,5,6-hexahydro[1,3]oxazino[3,4-*a*]-quinoline and its *trans*-1,4a-H-1-, *trans*-3,4a-H-3-, *cis*-3,4a-H-3-, *trans*-4,4a-H-4-, *cis*-4,4a-H-4-, and 10-methyl derivatives [93JCR(S)170] were recorded in CDCl₃ at room temperature at 67.97 MHz. The ¹³C NMR data for **37**–**39** were also reported (90CB803; 92T4937).

TABLE III

¹³C NMR DATA OF *trans* AND O-INSIDE *cis* CONFORMATIONS OF PERHYDROPYRIDO[1,2-*c*][1,3]OXAZINE(**20**, X = O) IN CD₂Cl₂-CFCl₃ AT 203 (92MRC129) AND ITS HYDROCHLORIDE SALT IN CDCl₃ AT ROOM TEMPERATURE (88MRC748), AND THOSE OF STEREOCHEMICALLY LOCKED PERHYDRO[3,2,1-*ij*][1,3]BENZOXAZINES (**25–28**) IN CDCl₃ AT ROOM TEMPERATURE (92MRC129) (ppm)

	C(1)	C(3)	C(4)	C(4a)	C(5)	C(6)	C(7)	C(8)			
<i>trans</i> 20 , X = O	86.7	68.0	32.5	60.8	32.1	24.0	25.0	49.1			
O-inside											
<i>cis</i>	86.2	68.4	24.0	53.4	30.0	18.7	26.0	44.6			
<i>trans</i>	83.3	67.5	29.3	62.7	29.8	21.9	22.3	49.0			
20 , HCl X = O											
O-inside											
<i>cis</i>	83.8	67.6	22.8	54.9	27.6	16.7	22.6	44.3			
	C(1)	C(3)	C(5)	C(6)	C(7)	C(7a)	C(8)	C(9)	C(10)	C(10a)	C(10b)
25	73.5	87.9	50.2	20.5	30.3	36.3	25.35	25.6	26.1	37.1	63.5
26	73.3	86.4	45.0	26.0	23.9	35.0	32.0	20.4	27.7	28.0	73.3
27	73.9	87.3	49.15	24.6	31.6	39.0	32.3	24.7	24.6	39.6	71.3
28	66.8	78.6	50.35	27.2	32.7	27.8	32.9	21.8	21.7	33.9	62.6

8. ¹⁵N NMR Spectroscopy

The low-temperature (−95°C) ¹⁵N NMR spectrum of perhydropyr-ido[1,2-*c*][1,3]oxazine (**20**, X = O) was measured in a 1:1 mixture of CS₂ and THF-*d*₆ [83OMR(21)203]. Only the ¹⁵N shift of the *trans*-fused con- former could be detected (δ¹⁵N 66.8 ppm down-field from anhydrous liquid ammonia). At 27°C the chemical shift of ¹⁵N was 65.5 ppm.

9. Mass Spectroscopy

5,5,7-Trimethyl-1*H*,3*H*,5*H*-pyrido[3,2,1-*ij*][3,1]benzoxazines were de- tected among the reaction products of 2,2,4-trimethyl-1,2-dihydroquinoline with formaldehyde and acetaldehyde by liquid chromatography–mass spec- troscopy (LC–MS) investigations (79MI1).

10. X-Ray Investigations

An X-ray crystal structural determination revealed that the 8-carboxyl group of *cis*-4*a*,8-*H*-1,3,4,4*a*,7,8-hexahydropyrido[1,2-*c*][1,3]oxazine-8- carboxylic acid is in a pseudoaxial position (81JA7573). The crystal struc- ture of 4-phenyl-2-{4-[4-(2-pyrimidinyl)piperazin-1-yl]butyl}-2,3,5,6,7,8- hexahydro-1*H*-pyrido[1,2-*c*][1,3]oxazine-1,3-dione was determined by an X-ray investigation (95ZK899).

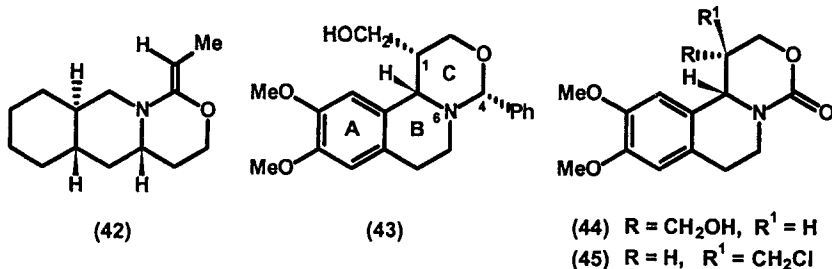
The absolute configuration of *cis*-1,3,4*a*-*H*-1-(4-nitrophenyl)-3-methyl- perhydropyrido[1,2-*c*][1,3]oxazine, having the 1*S*,3*R*,4*aS*,9*R* configuration, was determined in an X-ray diffraction study [71T2055; 72AX(B)37]. The chair-shaped heterocyclic rings adopt a *trans* conformation with equatorial methyl and aryl groups. The crystal structure of *cis*-1,4*a*-*H*-1-

TABLE IV
INTERATOMIC DISTANCE (pm) AND BOND ANGLES (°) IN TWO HETERO-ATOM-CONTAINING
RINGS OF 1-(4-BROMOPHENYL) DERIVATIVE OF PERHYDROPYRIDO[1,2-*c*][1,3]OXAZINE
AND PERHYDROPYRIDO[1,2-*c*][1,3]THIAZINE (**20**, X = O, S) WITH ESD^a IN
PARENTHESES (73MI1, 73MI2)

Bond length	X = O	X = S	Bond angle	X = O	X = S
N(9)–C(1)	148.6(8)	147.9(10)	C(4 <i>a</i>)–N(9)–C(1)	110.6(5)	111.4(6)
C(1)–X(2)	142.1(8)	183.6(7)	N(9)–C(1)–X(2)	109.3(5)	112.6(5)
X(2)–C(3)	145.2(9)	181.3(9)	C(1)–X(2)–C(3)	111.5(5)	97.1(3)
C(3)–C(4)	152.9(10)	148.8(16)	X(2)–C(3)–C(4)	108.1(6)	111.7(8)
C(4)–C(4 <i>a</i>)	151.2(10)	151.0(11)	C(3)–C(4)–C(4 <i>a</i>)	110.3(5)	113.0(8)
C(4 <i>a</i>)–N(9)	148.6(8)	146.7(9)	C(4)–C(4 <i>a</i>)–N(9)	109.8(5)	113.5(6)

^a Estimated standard deviation.

(*p*-bromophenyl)perhydropyrido[1,2-*c*][1,3]oxazine was also determined by means of X-ray diffraction examinations (73MI1) (Table IV). The *Z* geometry of the 1-ethylidene group in **42** was confirmed in an X-ray diffraction investigation (80HCA1158).



The conformations and configurations of 1,6,7,11*b*-tetrahydro-2*H*,4*H*-[1,3]oxazino[3,4-*b*]isoquinolines (**43**–**45**) were likewise determined by X-ray analysis (90CB803, 90T4039). The opposite signs of the torsion angles C(11*a*)–C(11*b*)–N(5)–C(6) and C(1)–C(11*b*)–N(5)–C(4) indicate the *trans* junction of the pyridine and oxazine rings in **43**, a *transoid* ring junction in **44**, and a *cisoid* ring junction in **45**.

B. PYRIDO[1,2-*c*][1,3]THIAZINES AND THEIR BENZO DERIVATIVES

1. Dipole Moment Investigations

The dipole moment of perhydropyrido[1,2-*c*][1,3]thiazine (**20**, X = S) was calculated from measurements in benzene at 25°C [76JCS(P2)418]. These investigations indicated that perhydropyrido[1,2-*c*][1,3]thiazine exists as an 80:20 equilibrium mixture of the *trans*-fused and S-inside *cis*-fused conformers, the S-outside *cis*-fused conformer contributing only ~ 1% to the equilibrium (Scheme 5).

2. IR Spectroscopy

Pronounced Bohlmann bands in the region 2800–2600 cm⁻¹ of the IR spectra of perhydropyrido[1,2-*c*][1,3]thiazine and its *cis*-1,4*a*-H-1-phenyl, *cis*- and *trans*-3,4*a*-H-3-methyl, *trans*-4*a*,5-H-5-methyl, *cis*-4*a*,8-H-8-methyl, *cis*-1,4*a*-H-*trans*-5-H-5-methyl-1-phenyl, and *trans*-4*a*,7-H-7-ethyl derivatives indicate the predominance of the *trans*-fused conformation [70T3941; 82OMR(20)239]. The absence of marked absorbance in the same region

of the IR spectra of 1,2,4,5,6,11*b*-hexahydro[1,3]thiazino[4,3-*a*]isoquinoline and its *cis*-4,11*b*-H-4-(*p*-nitrophenyl) derivative suggests the presence of a *cis*-fused conformation of the heterorings [76OMR(8)258; 77JCS(P2)370].

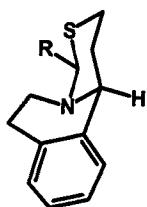
3. ¹H NMR Spectroscopy

Differences between the stereochemistry of perhydropyrido[1,2-*c*][1,3]thiazines and that of the closely related perhydropyrido[1,2-*c*][1,3]oxazines are expected to arise principally from the long C—S bond (181 pm) as compared with the C—O bond length of 141 pm, and also from differences in bond angles and in torsional interactions involving the heteroatoms. The longer C—S bonds in perhydropyrido[1,2-*c*][1,3]thiazine result in a lower interaction in the S-inside *cis*-fused conformer in comparison with the O analog, which increases the contribution of the S-inside *cis*-fused conformer to the equilibrium. The predominant conformation of perhydropyrido[1,2-*c*][1,3]thiazine (**20**, X = S) is the *trans*-fused one (Scheme 5) (70T3941).

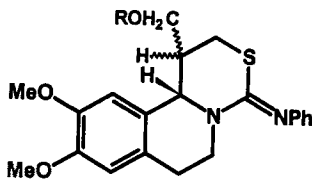
1-H_{eq} in perhydropyrido[1,2-*c*][1,3]thiazine (**20**, X = S) absorbs at higher field (3.60 ppm in CCl₄) than 1-H_{ax} (3.91 ppm), as does 4-H_{eq} (4.04 ppm in CDCl₃) in 1,2,4,5,6,11*b*-hexahydro[1,3]thiazino[4,3-*a*]isoquinoline than 4-H_{ax} (4.68 ppm). This is in contrast with the situation in perhydropyrido[1,2-*c*][1,3]oxazine (4.70 and 3.52 ppm, respectively) and 1,2,4,5,6,11*b*-hexahydro[1,3-*a*]oxazino[4,3-*a*]isoquinoline (4.52 and 4.32 ppm in C₆D₆), which can be interpreted in terms of the differences between the C—S and C—O bond anisotropies [70T3941; 77JCS(P2)370]. A coupling of 1.6 Hz is observed between 1-H_{eq} and 4-H_{eq}, which suggests marked deviations from the chair conformation for the 1,3-thiazine ring (70T3941).

Conformational analysis demonstrated that the predominant conformation of the *cis*-1,4*a*-H-1-phenyl, *cis*- and *trans*-3,4*a*-H-3-methyl, *trans*-4*a*,5-H-5-methyl, *cis*-4*a*,8-H-8-methyl, and *trans*-4*a*,7-H-7-ethyl derivatives of perhydropyrido[1,2-*c*][1,3]thiazine is the *trans*-fused one, whereas for the *cis*-4*a*,5-H-5-methyl and *cis*-4*a*,7-H-7-methyl derivatives it is the S-inside *cis*-fused conformation [70T3941; 82OMR(20)239]. The chemical shift differences (1.13 and 0.49 ppm) between the C-8 methylene protons of *trans*-4*a*,7-H-7-ethyl- and *cis*-4*a*,7-H-7-ethylperhydropyrido[1,2-*c*][1,3]thiazines are in accord with exclusive existence in the *trans*-fused and in the *cis*-fused ring conformations, respectively [82OMR(20)239].

1,2,4,6,7,11*b*-[1,3]Thiazino[4,3-*a*]isoquinolone and its *cis*-4,11*b*-H-4-(4-nitrophenyl) derivative (**46**, R = H, 4-NO₂Ph) predominantly adopt the S-inside *cis*-fused conformation in CDCl₃, which is favored by the generalized anomeric effect [76OMR(8)258; 77JCS(P2)370].



(46)



(47)

The relative configurations and the predominant conformation of 1-epimers of 1,2,4,6,7,11*b*-[1,3]thiazino[4,3-*a*]isoquinolin-4-imines (**47**) were determined by the use of ^1H NMR spectroscopy (90CB803).

4. ^{13}C NMR Spectroscopy

Conformational analysis of perhydropyrido[1,2-*c*][1,3]thiazine (**20**, X = S) and its *trans*- and *cis*-4*a*,7-H-7-ethyl derivatives indicated that *trans*-4*a*,7-H-7-ethylperhydropyrido[1,2-*c*][1,3]thiazine and the *cis*-4*a*,7-H-7-ethyl analog exist exclusively in the *trans*-fused and the S-inside *cis*-fused conformation, respectively, containing the ethyl group in the equatorial positions, whereas the parent perhydropyrido[1,2-*c*][1,3]thiazine in CDCl_3 at 25°C is a ca. 25:75 mixture of the S-inside *cis*-fused and *trans*-fused conformations. At -75°C, where the interconversion is slow in a 1:1 mixture of CS_2 and $\text{THF-}d_8$, the signals of both conformers of perhydropyrido[1,2-*c*][1,3]thiazine can be detected. The ^{13}C NMR spectrum shows the presence of 64% of the *trans*-fused and 36% of the S-inside *cis*-fused conformer [82OMR(20)239].

The ^{13}C NMR chemical shifts of 1-epimers of the *N*-phenyl-1-hydroxymethyl- and 1-acyloxymethyl-9,10-dimethoxy-1,2,4,6,7,11*b*-hexahydro[1,3]thiazino[4,3-*a*]isoquinolin-4-imines (**47**) were measured in CDCl_3 (90CB803).

5. ^{15}N NMR Spectroscopy

At -95°C, the *cis-trans* interconversion of the conformers of perhydropyrido[1,2-*c*][1,3]thiazine (**20**, X = S) is frozen, and the ^{15}N NMR spectrum of the S-inside *cis*-fused conformer of perhydropyrido[1,2-*c*][1,3]thiazine reveals a shielding of the nitrogen by 23.0 ppm relative to the *trans*-fused conformer ($\delta_{15\text{N}}$ 66.9 ppm downfield from the signal of anhy-

drous liquid ammonia) in a 1:1 mixture of CS₂-THF-*d*₆. This enhanced chemical shift difference reflects both the β -substituent effect of C-4 methylene and the generalized anomeric effect differences between the *trans*- and *cis*-conformers. At 27°C, a time-averaged chemical shift of 58.3 ppm was measured, which suggests the presence of a 38:62 equilibrium mixture of the S-inside *cis*-fused and *trans*-fused conformations [83OMR(21)203].

6. X-Ray Investigations

An X-ray structural determination of 1-(4-bromophenyl)perhydropyrido[1,2-*b*][1,3]thiazine revealed that both fused rings adopt almost ideal chair conformations (73MI2). A comparison of the corresponding data on 1-(4-bromophenyl)perhydropyrido[1,2-*b*][1,3]oxazine (73MI1) and 1-(4-bromophenyl)perhydropyrido[1,2-*b*][1,3]thiazine showed that the C—C bond lengths and bond angles are similar, with the exception of the C(3)—C(4) bond (152.9 pm in pyrido[1,2-*c*][1,3]oxazine and 148.8 pm in pyrido[1,2-*c*][1,3]thiazine) (Table IV). In pyrido[1,2-*c*][1,3]oxazine there is some puckering around the oxygen, but in pyrido[1,2-*c*][1,3]thiazine there is a degree of flattening around the sulfur. The lengths of the C(1)—S and S—C(2) bonds are 183.6 and 181.3 pm, respectively, whereas those of the C(1)—O and O—C(2) bonds are 142.1 and 145.2 pm, respectively. The phenyl ring is perpendicular to the best plane of the bicycle.

C. PYRIDO[1,2-*c*]PYRIMIDINES AND THEIR BENZO DERIVATIVES

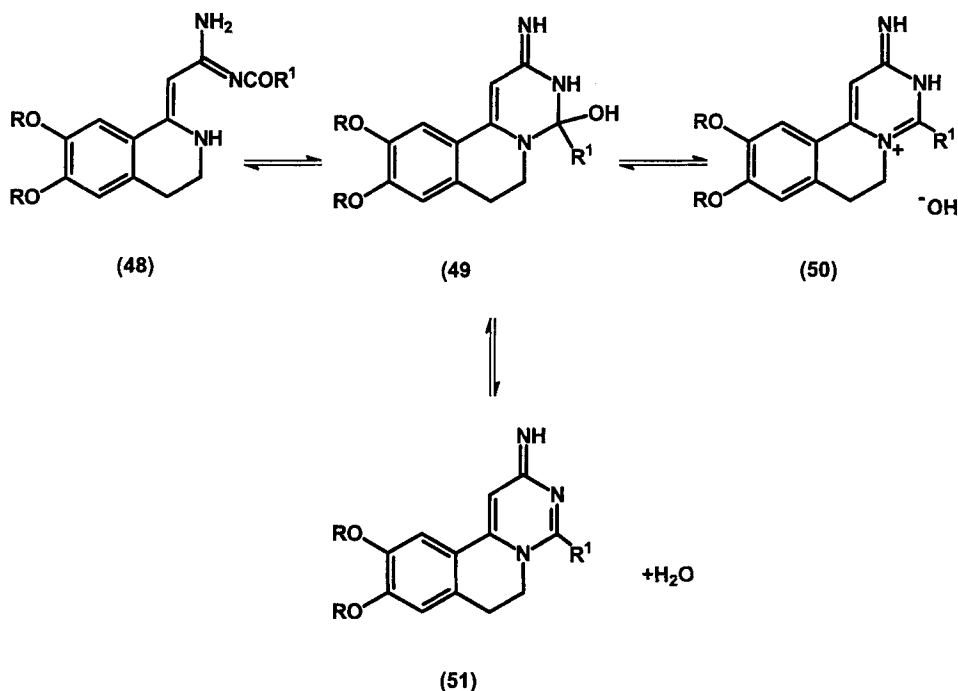
1. Thermodynamic Aspects

A selective reversed-phase HPLC method was developed for studies on the antiarrhythmic hexahydro-3*H*-pyrido[1,2-*c*]pyrimidin-3-one (**18**) and its 4-epimer (87MI7).

The protonation constants ($pK_{a1} = 4.8$ and $pK_{a2} = 10.3$) of **18** were determined by titration (87MI2). The protonation constant of 2-amino-4-aryl-6,7-dihydropyrido[6,1-*a*]isoquinolinium chlorides were determined in 50% aqueous ethanol, and their pK_a s were calculated via Eq. 1 (82KGS1095).

$$pK_a = 10.08 - 1.43 \sigma_n, \quad r = 0.97, \quad s = 0.15 \quad (1)$$

2-Imino-4-substituted-6,7-dihydropyrimido[6,1-*a*]isoquinolines yield an equilibrium system involving the tautomeric forms of pseudobases **48**, **49**, and **50** and anhydro base **51** (see Scheme 8) [90CB493; 91CB111; 94H(37)2051].



SCHEME 8

2. Theoretical Calculations

The electron densities, the bond orders, the first six energies, and the oscillator strengths of the pyrido[1,2-*c*]pyrimidinium cation were calculated using the SCFMO semiempirical version of the PPP method. Protonation is expected to take place on the nonbridgehead N atom, and position 1 is predicted to be most reactive toward nucleophilic substitution (68TCA417).

The bioactive conformation of 6-dipropylamino-1,2,3,5,6,7-hexahydropyrido[3,2,1-*ij*]quinazolin-3-one was predicted by Compass algorithm for 5-HT_{1A} binding (95JMC1295).

3. Dipole Moment Investigations

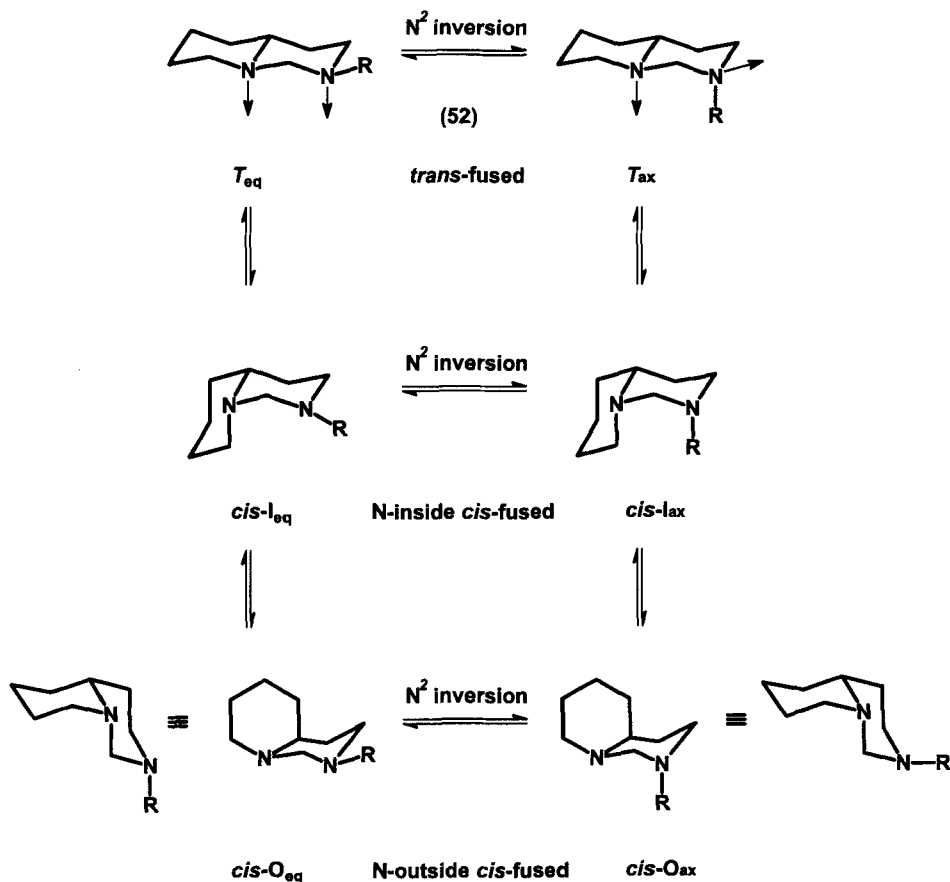
The dipole moments of 2-methyl- and 2-*tert*-butylperhydropyrido[1,2-*c*]pyrimidine (**52**, R = Me and *t*Bu) (1.40 and 1.47 D, respectively) were determined in benzene [76JCS(P2)418]. From the calculated dipole moment data, it was concluded that the 2-*tert*-butyl derivative exists almost exclu-

sively in the *trans*-fused conformation T_{eq} , whereas the 2-methyl derivative exists predominantly (ca. 75%) in the same conformation (T_{eq}); these conclusions proved to be in good agreement with the experimental data (see Section II,C,6,a).

4. UV Spectra

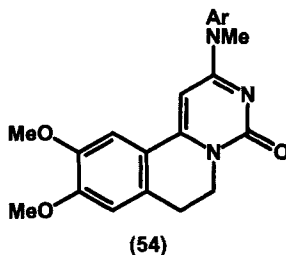
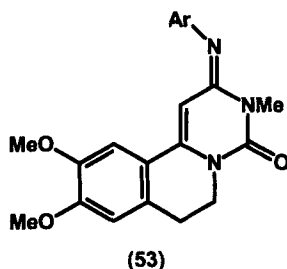
The pH dependence of the tautomerism of 4-iminopyrimido[6,1-*a*]isoquinolines **49–51**, depicted in Scheme 8, was investigated by UV spectroscopy (90CB493).

In the UV spectra bands at 275, 283.8, and 340 nm are characteristic for 3-methyl-2-(*N*-arylimino)-2, 3, 6,7-tetrahydro-4*H*-pyrimido[6,1-*a*]isoquino-



SCHEME 9

lin-4-ones (**53**), and bands at 271.5 and 281 nm for isomeric 2-(*N*-aryl-*N*-methylimino)-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-ones (**54**) (84JMC1470).



5. IR Spectra

The appearance of Bohlmann bands in the IR spectrum of perhydropyr-ido[1,2-*c*]pyrimidine indicated that this compound exists predominantly in the *trans*-fused conformation (69JHC181), but the application of Bohlmann's IR criterion to perhydropyr-ido[1,2-*c*]pyrimidines is greatly complicated by the presence of the two N atoms and in some cases the α -H atoms of the 2-alkyl group (70T701).

On the basis of the weak Bohlmann bands in their IR spectra, *cis*-fused ring conformations were assigned to *cis*-7,4*a*-H-2,7-dimethyl- and *cis*-5,4*a*-H-2,5-dimethylperhydropyr-ido[1,2-*a*]pyrimidin-3-ones [72JCS(P2)1920], and to 1,6,7,11*b*-tetrahydro- and 1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-2-ones (84JHC149). The 2-methyl-, *cis*-8,4*a*-H-2,8-dimethyl-, *trans*-7,4*a*-H-2,7-dimethyl-, and *trans*-5,4*a*-H-2,5-dimethylperhydropyr-ido[1,2-*c*]pyrimidin-3-ones displayed marked Bohlmann bands, and the *trans*-fused ring conformations were assigned [72JCS(P2)1920]. The strong Bohlmann bands in the IR spectrum of 2,3,4,4*a*,5,6-hexahydro-1*H*-pyr-ido[1,6-*a*]quinoline indicated the predominance of the *trans*-fused ring conformation with an equatorial *N*-methyl group [79JCS(P2)581].

In the IR spectra three well-resolved bands at 1635, 1625, and 1615 cm^{-1} are characteristic for 3-methyl-2-(*N*-arylimino)-2,3,6,7-tetrahydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-ones (**53**), in contrast to broad bands at 1661, 1645, and 1637 cm^{-1} for isomeric 2-(*N*-aryl-*N*-methylimino)-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-ones (**54**) (84JMC1470).

6. ^1H NMR Spectra

a. *Fully Saturated Ring Systems.* There are six possible all-chair conformations of perhydropyr-ido[1,2-*c*]pyrimidines (**52**), which are interconvert-

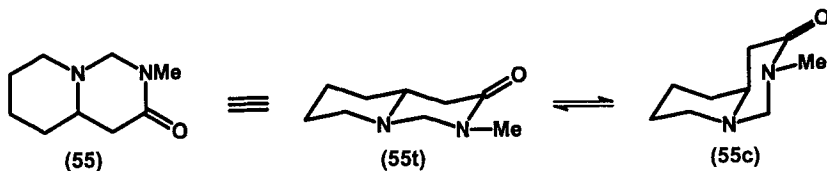
ible by ring inversion and N² inversion (Scheme 9). Two of these (*cis*- I_{ax} and *cis*- O_{ax}) may be neglected because of the presence of severe nonbonded interactions, and their contributions to the equilibrium will be neglected.

In conformation T_{eq} , the unfavorable dipole–dipole interaction between the N atoms may be relieved by the inversion of N(2) (conformation T_{ax}). Conformation T_{ax} is destabilized by *gauche*-butane and *gauche*-*n*-propylamine interactions, which are expected to be ca. 1.7 kcal mol⁻¹. The O-outside *cis* conformer, *cis*- O_{eq} , should be higher in energy than the *trans* conformer T_{eq} by approximately the value for the *cis*–*trans*-quinolizidine, ΔG° , and should therefore contribute only ca. 1% to the equilibrium at 25°C. The difference between the *trans* conformer T_{ax} and the N-inside *cis*-fused conformer, *cis*- I_{eq} , is approximately one *gauche*-butane interaction (ca. 0.9 kcal mol⁻¹) in favor of T_{ax} , and they should be in an equilibrium ratio of ca. 4:1 at 25°C. The equilibrium energy difference between T_{eq} and T_{ax} was expected to be of the order of 0.3 kcal mol⁻¹. On this basis, the equilibrium proportions for 2-methylperhydropyrido[1,2-*c*]pyrimidine (**52**, R = Me) are ca. 75% T_{eq} , 20% T_{ax} , and 5% *cis*- I_{eq} [76JCS(P2)418].

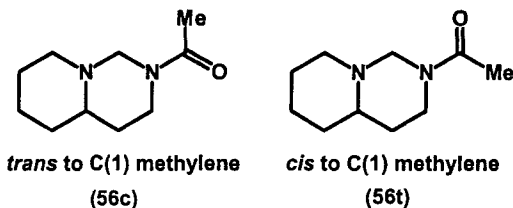
The geminal coupling constant for the C(1) methylene group depends on the orientation of the C(1)–H bonds with respect to the N atom lone pairs, and it is suitable for the conformational analysis of perhydropyrido[1,2-*c*]pyrimidines. Thus, perhydropyrido[1,2-*c*]pyrimidines (**52**) existing in the *trans*-fused ring conformation (T_{eq}) with an equatorial N(2) alkyl group are expected to have a larger (smaller absolute value) J_{gem} for the C(1) methylene group (ca. –8.5 Hz versus –11.2 Hz) than those compounds in which either the ring fusion is *trans* and the N(2) alkyl group is axial (T_{ax}) or the ring fusion is *cis* (*cis*- I_{eq}) [76JCS(P2)418].

Because of the presence of the bulky substituent at position 2, 2-*tert*-butylperhydropyrido[1,2-*c*]pyrimidine (**52**, R = *t*Bu) exists predominantly in conformation T_{eq} and has a J_{gem} of –8.5 Hz for the C(1) methylene group (70T701). Later, a value of –8.8 Hz was determined in a more accurate determination from the 220-MHz spectrum [76JCS(P2)418]. As other 2-alkylperhydropyrido[1,2-*c*]pyrimidines have J_{gem} values between –8.4 and –8.6 Hz for the C(1) methylene group, they adopt predominantly the *trans*-fused conformation with an equatorial substituent (T_{eq}) (70T701). For 2-methylperhydropyrido[1,2-*c*]pyrimidine (**52**, R = Me), a J_{gem} of –9.2 Hz was determined, which corresponded to ca. 75% of the *trans*-fused conformation, T_{eq} [76JCS(P2)418]. There is a long-range coupling of ca. 1.8 Hz between 1- H_{eq} and 3- H_{eq} in 1-alkylperhydropyrido[1,2-*c*]pyrimidines (70T701). The 3-phenyl derivative (**52**, R = Ph) exists predominantly as the *trans*-fused conformer T_{eq} , but J_{gem} for the C(1) methylene group is 10.5 Hz because of overlap between the π -electrons of the phenyl group and the axial lone pair of N(2) (70T701).

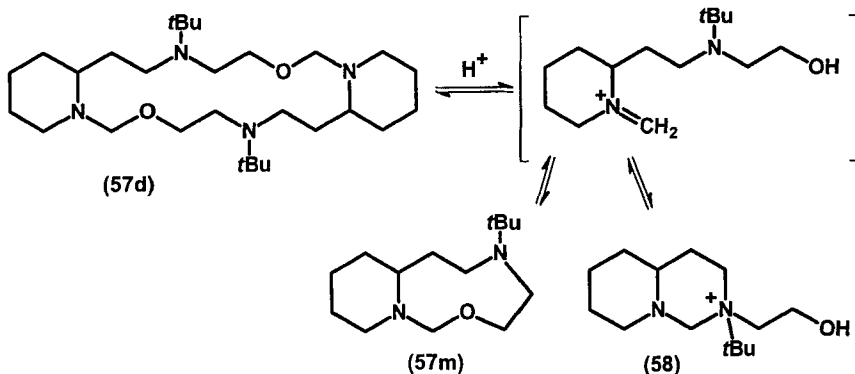
For the J_{gem} values for the C(1) methylene group (between -8.5 and -8.8 Hz), it was concluded that *cis*-3,4*a*-H-2-methyl-3-alkyl- (methyl and ethyl), *trans*-4,4*a*-H-2,4-dimethyl-, *cis*-4*a*8,-H-2,8-dimethyl-, and 2-*tert*-butyl-8-methylperhydropyrido[1,2-*c*]pyrimidines exist predominantly as the *trans*-fused conformer T_{eq} , with an equatorial C-alkyl group, whereas *cis*-4,4*a*-H-2,4-dimethylperhydropyrido[1,2-*c*]pyrimidine exists predominantly as the conformer T_{eq} with an axial C-methyl group. For *trans*-3,4*a*-H-2-methyl-3-alkylperhydropyrido[1,2-*c*]pyrimidines, the J_{gem} values of the C(1) methylene groups (-10.8 and -11.4 Hz) and the long-range coupling between 1- H_{eq} and 3- H_{eq} indicate the predominant presence of *trans*-fused conformer T_{ax} with an axial C(-3) alkyl group. *trans*-4*a*,8-H-2,8-Dimethyl- and 2-*tert*-butyl-8-methylperhydropyrido[1,2-*c*]pyrimidines have J_{gem} values of -9.9 and -9.8 Hz for the C(1) methylene protons, which indicate the presence of conformational mixtures containing appreciable amounts of the conformations *cis*- I_{eq} and T_{eq} (70T701).



The J_{gem} value of 9.0 Hz for the C(1) methylene protons of 2-methylperhydropyrido[1,2-*c*]pyrimidin-3-one (55) in CCl_4 , when the nonbridgehead N atom with its lone pair of electrons is incorporated in an amide group, points to the presence of ca. 16% *cis*-fused conformer (55c) in equilibrium with the *trans*-fused conformer (55t) [72JCS(P2)1920]. *cis*-4*a*,7-H-2,7-Dimethylperhydropyrido[1,2-*c*]pyrimidin-3-one ($J_{\text{gem}} -10.8$ Hz) exists as ca. 72% of the *cis*-fused conformer in equilibrium with 28% of the *trans*-fused one. *cis*-4*a*,5-H-2,5-Dimethylperhydropyrido[1,2-*c*]pyrimidin-3-one ($J_{\text{gem}} -11.7$ Hz) exists predominantly in the *cis*-fused conformation, and *cis*-4*a*,8-H-, *trans*-4*a*,7-H-, and *trans*-4*a*,5-H-2,X-dimethylperhydropyrido[1,2-*c*]pyrimidin-3-ones ($J_{\text{gem}} -8.5$ and -8.7 Hz) in the *trans*-fused ones. J_{gem} for the C(4) methylene protons (-11.3 Hz) indicates a conformation such that the nodal plane of the amide carbonyl bisects the C(4) H_2 internuclear axis.



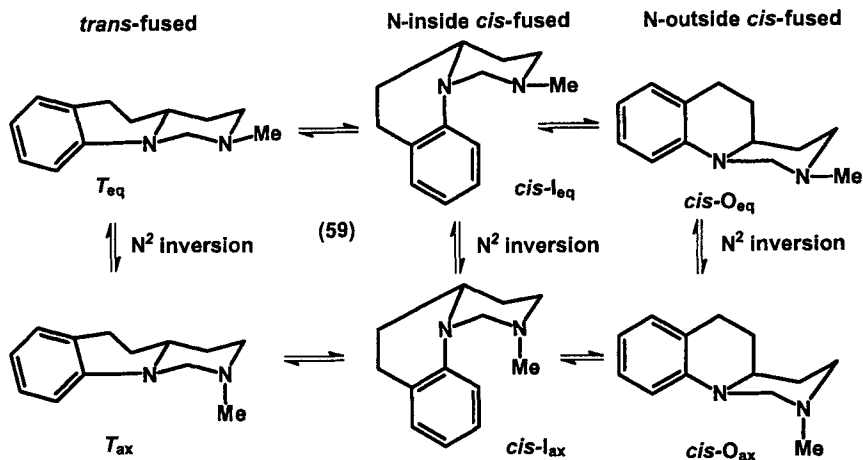
The room-temperature ^1H NMR spectrum of 2-acetylperhydropyr-ido[1,2-*c*]pyrimidine exhibits signals arising from both rotational isomers (**56c** and **56t**), as a result of restricted rotation about the N—C(=O)Me bond. The *cis* and *trans* isomers **56c** and **56t** could be distinguished on the basis of J_{gem} for the protons of the methylene group adjacent to the amido N, and the chemical shift of 1- H_{eq} [73OMR(5)397].



The ^1H NMR spectrum of **57d** in CDCl_3 – CFCl_3 solution at 19°C indicates an equilibrium mixture containing 45% of the pyrido[1,2-*c*]pyrimidinium ion (**58**), 27% of the dimer (**57d**), and 28% of the monomer (**57m**) [79JCS(P2)504]. At -45°C , only the signals of the dimer (**57d**) could be assigned in the spectrum.

b. *Partly Saturated Ring Systems.* Of the six all-chair conformations of 2-methyl-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrimido[1,6-*a*]quinoline (**59**), the high-energy *cis*-fused conformations (*cis*- I_{ax} , *cis*- O_{ax} , *cis*- I_{eq} , and *cis*- O_{eq}) cannot be expected to contribute significantly to the equilibrium (Scheme 10). The *trans*-fused conformations (T_{eq} and T_{ax}) differ only in terms of the unfavorable generalized anomeric effect present in T_{eq} and the *gauche*-*n*-propylamine interaction in T_{ax} . Both conformers are stabilized further by the delocalization of the bridgehead N atom lone pair into the aromatic π -electron system of the phenyl ring. J_{gem} (-11.1 Hz) for the C(1) methylene protons indicates that 2-methyl-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrimido[1,6-*a*]quinoline in CDCl_3 establishes a conformational equilibrium involving ca. 81% T_{eq} and 19% T_{ax} [79JCS(P2)581].

Of the six all-chair conformations of 2-methyl-1,3,4,6,7,11*b*-hexahydro-2*H*-pyrido[6,1-*a*]isoquinoline (**60**), the *cis*- I_{ax} , *cis*- O_{eq} , and *cis*- O_{ax} conformations could be discounted because they suffer from a number of nonbonded interactions (Scheme 11). The basic difference between the *trans*-fused and *cis*-fused conformations is that in the *trans*-fused ring conformations (T_{eq} and T_{ax}) the perhydropyrimidine ring is fused onto the tetrahydropyridine



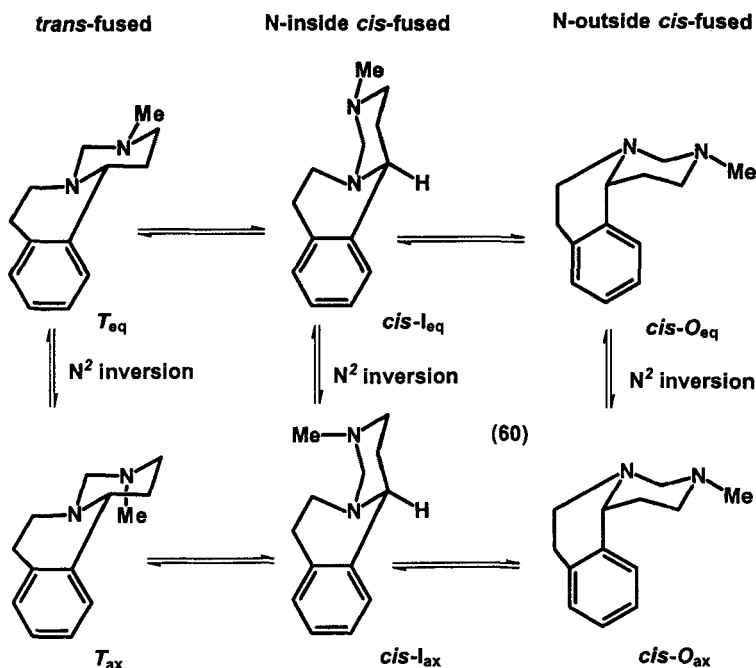
SCHEME 10

ring, by utilization of the pseudoequatorial and equatorial bonds of the tetrahydropyridine ring, and this increases the strain in the fused system. This *trans*-ring fusion strain is not present in the conformation *cis*-I_{eq}, where fusion of the perhydropyrimidine ring can readily occur, since the fusion involves the pseudoequatorial and axial (or equatorial and pseudoaxial) bonds. The J_{gem} value of the C(4) methylene protons (-9.8 Hz) indicates the presence of an equilibrium between ca. 54% of conformation T_{eq} and 46% of conformations *cis*-I_{eq} and T_{ax} , in which one of the N lone pairs bisects the C(4) methylene protons [77JCS(P2)370].

The J_{gem} value (-10.1 Hz) of the C(4) methylene protons suggests that 3-methyl-1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-2-one (**61**) adopts an equilibrium involving about 53% of the *trans*-fused and 47% of the *cis*-fused conformer (Scheme 12). The vicinal coupling constants relating to 11*b*-H ($J_{11b,1ax} \approx 11.5$ Hz, $J_{11b,1eq} \approx 4.6$ Hz) rule out the presence of the N-outside *cis*-fused conformer (91MRC1040). 3-Methyl and 3-phenyl-1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-2,4-diones adopt a *trans*-fused conformation (91MRC1040).

The coupling constants between 11*b*-H and the C(1) methylene protons (14 and 6 Hz, and 9 and 3 Hz) for 9,10-dimethoxy-4-phenyl-1,6,7,11*b*-tetrahydro- and 1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines indicate the predominance of the N-inside *cis* conformation (84JHC149).

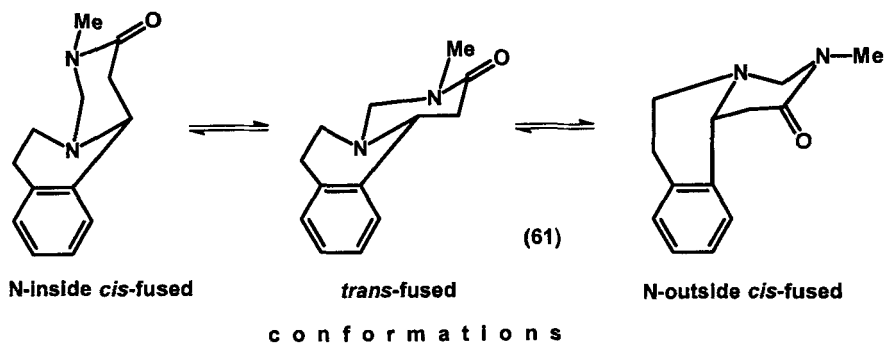
The ^1H NMR spectra of 3-methyl- and 3-phenyl-1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-2,4-diones in CDCl_3 are very similar to each other, and the magnitudes of the coupling constants involving the



SCHEME 11

C(6) and C(1) methylene protons are consistent with the *trans*-fused conformation (91MRC1040).

In the ^1H NMR spectra downfield shifts for the NCH_3 and H-1 protons are characteristic for 3-methyl-2-[*N*-(2,4,6-trimethylphenyl)imino]-2,3,6,7-tetrahydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-one (**53**, Ar = 2,4,6-trimethylphenyl) relative to those for corresponding protons in 2-[*N*-(2,4,6-trimethyl-



SCHEME 12

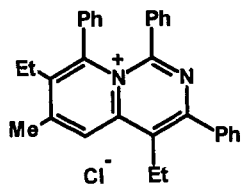
phenyl)-*N*-methylimino]-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-one (**54**, Ar = 2,4,6-trimethylphenyl) (84JMC1470).

7. ^{13}C NMR Spectra

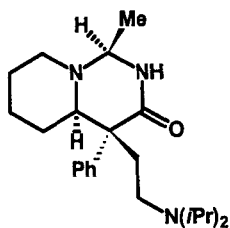
^{13}C NMR data on 2-oxo-, 3-methyl-, and 3-phenyl-2,4-dioxo-1,3,4,6,7,11*b*-hexahydropyrimido[6,1-*a*]isoquinolines have been measured in CDCl_3 (91MRC1040). The structures of 3-amino-4-substituted 1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-2-ones have similarly been investigated by means of ^{13}C NMR spectroscopy (90JHC957).

8. X-Ray Investigations

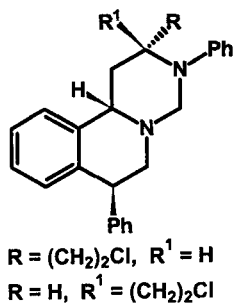
The structures of pyrido[1,2-*c*]pyrimidinium chloride (**62**) (91KGS1556), hexahydro-3*H*-pyrido[1,2-*c*]pyrimidin-3-ones (**18** and **63**) (85JMC1285), and 1,3,4,6,7,11*b*-hexahydropyrimido[6,1-*a*]isoquinolin-4-ones (**64**) (82TL-2829; 83JOC5074) have been determined by X-ray crystallography. The structure of a wild-type human immunophilin FKBP12 (a member of a ubiquitous family of proteins) complexed with benzyl *trans*-4*a*,8-*H*-1-oxo-2-propylperhydropyrido[1,2-*c*]pyrimidine-9-carboxylate was determined by X-ray investigations (96JMC1872).



(62)



(63)



R = $(\text{CH}_2)_2\text{Cl}$, R' = H
R = H, R' = $(\text{CH}_2)_2\text{Cl}$

(64)

The X-ray analysis revealed that **53** (Ar = 2,4,6-trimethylphenyl) exists as the *Z* isomer with the mesitylene moiety perpendicular to the plane of the pyrimido[6,1-*a*]isoquinoline skeleton away from the *N*-methyl group (84JMC1470).

X-ray diffraction studies showed that protonation occurred on the 2-imino group of 2-imino-9,10-dimethoxy-4-phenyl-6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinoline in the solid state, and not on N(3) as in $\text{DMSO}-d_6$ solution (90CB493).

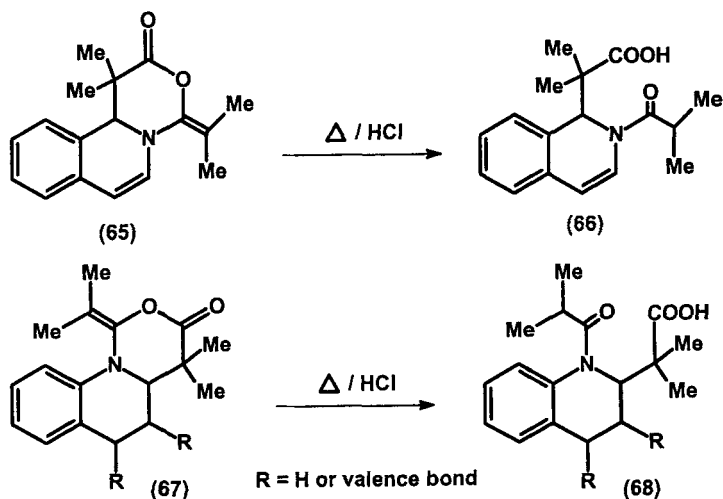
III. Reactivity

A. PYRIDO[1,2-*c*][1,3]OXAZINES AND THEIR BENZO DERIVATIVES

1. Ring Opening

The presence of a substituent at position 1 of perhydropyrido[1,2-*c*][1,3]oxazines decreases the stability of the bicycle (54JA2431). Hydrolysis of perhydropyrido[1,2-*c*][1,3]oxazines [56CLY1180; 57CLY927; 60JOC2028; 70LA(737)24] or their 1-oxo derivatives (84JA3240; 91TL4371; 93JA8851) gave 2-(2-hydroxyethyl)piperidines, whereas that of pyrido[3,2,1-*ij*][3,1]benzoxazin-3-ones and the -1,3-dione yielded 8-hydroxy-methyl-1,2,3,4-tetrahydroquinolines (87EUP239129; 90CPB1575) and 1,2,3,4-tetrahydroquinoline-8-carboxylic acid (64M59), respectively. The rate of the solvolysis of *trans*-3,4a-*H*-3-substituted perhydropyrido[1,2-*c*][1,3]oxazines was higher than that of *cis*-3,4a-*H* epimers (57CLY927). The *trans*-3,4a-*H*-3-substituted perhydropyrido[1,2-*c*][1,3]oxazines, containing the R substituent in an axial position, were hydrolyzed faster than the 3-epimeric derivatives in 2 *N* acetic acid at 25°C in the presence of dimedone [70LA(737)24].

Treatment of *r*-4a,*c*-5a,*t*-9a-*H*-1-ethylideneperhydro[1,3]oxazino[3,4-*b*]isoquinoline (42) with water in methylene chloride gave 2-(*trans*-perhydroisoquinolin-3-yl)ethyl propionate (80HCA1158).



Acidic hydrolysis of [1,3]oxazino[4,3-*a*]isoquinolin-2-one (65) and [1,3]oxazino[3,4-*a*]quinoline-3-ones (67) in boiling 5% hydrochloric acid

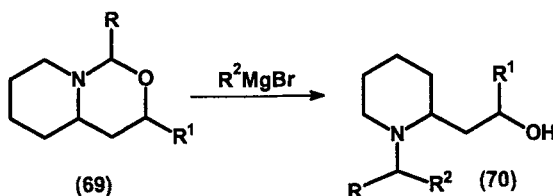
furnished 3-substituted 2,2-dimethylpropionic acids **66** and **68**, respectively [66JCS(CC)262; 67JCS(C)1569].

The reactions of 3,5,6,7-tetrahydro-1*H*-pyrido[3,2,1-*ij*][3,1]benzoxazine-1,3-dione with amines in dioxane led to *N*-substituted 1,2,3,4-tetrahydroquinoline-8-carboxamides (78JHC645; 79JHC897).

Depending on the reaction conditions, treatment of 4-hydroxymethyl-3,4-dihydro-1-oxo-1*H*-pyrido[2,1-*c*][1,3]oxazinium chloride with NH_3 afforded either 4-hydroxymethyl-1,3-dihydropyrido[2,1-*c*][1,3]oxazin-1-one or different ring-opened products (92JOC5764).

Catalytic hydrogenation of perhydropyrido[1,2-*c*][1,3]oxazines over Pt (54JA2431) and their treatment with aqueous formic acid (54JA2431) or with LAH [57CLY927; 58CLY2081; 67RZC1389; 71LA(753)27; 85T2891; 87T935; 93JOC5035; 96SL100] yielded 1-substituted 2-(2-hydroxyethyl)piperidines. Reductive ring-opening of 1,6,7,11*b*-tetrahydro-2*H*,4*H*-[1,3]oxazino[4,3-*a*]isoquinolines (66AP997; 90T4039; 91ACH375) and their 1-oxo derivatives (90T4039) with LAH resulted in the formation of 2-(*N*-alkyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethanols.

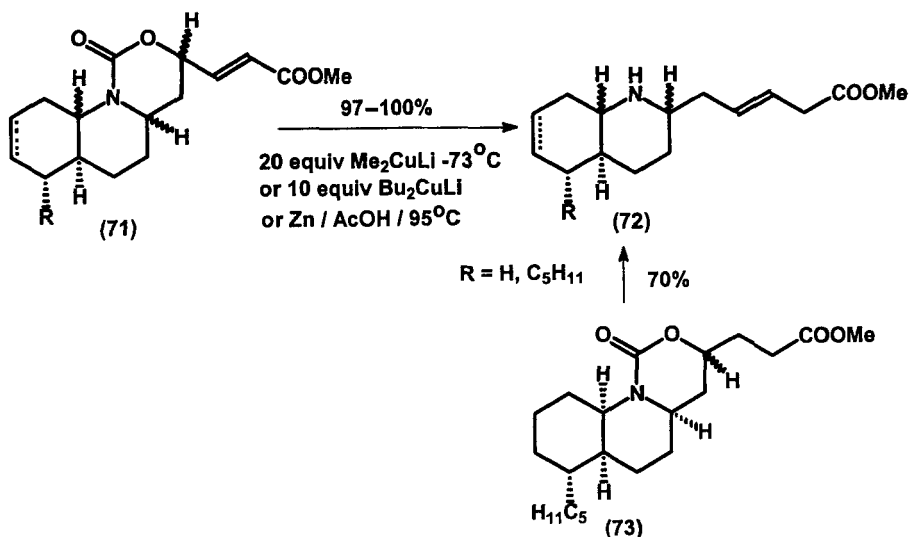
The boiling of optically active 3-deuterio-3-*p*-methoxyphenylperhydropyrido[1,2-*c*][1,3]oxazine in ethanol in the presence of 20% w/w of 10% Pd/C catalyst yielded *N*-formyl-2-(2-deuterio-2-*p*-methoxyphenylethyl)piperidine with no deuterium loss [72JCS(CC)1152].



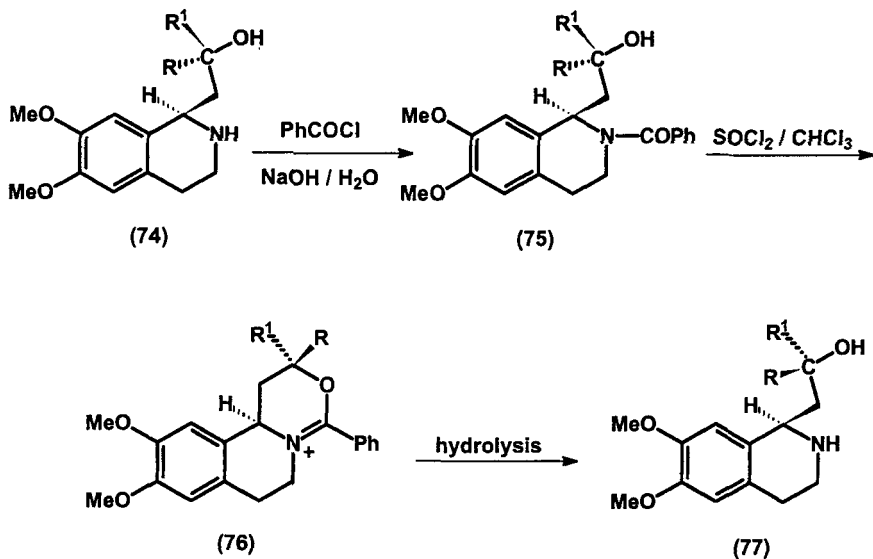
The reaction of 1,3-disubstituted perhydropyrido[1,2-*c*][1,3]oxazines (**69**) and 7-(benzothiazol-1-yl)-6,7-dihydro-1*H*,3*H*,5*H*-pyrido[3,2,1-*ij*][3,1]benzoxazine with Grignard reagents led to 2-(*N*-substituted 2-piperidyl)ethanols (**70**) (50JA358; 58CLY2081) and 1-benzyl-4-(benzotriazol-1-yl)-8-hydroxymethyl-1,2,3,4-tetrahydroquinoline (95JOC3993), respectively.

Ring opening of 9,10-dimethoxy-1,2,4,5,6,11*b*-hexahydro[1,3]oxazino[4,3-*a*]isoquinoline occurred on treatment with acyl chlorides or with hydrogen cyanide in ethanol, to give 6,7-dimethoxy-1-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline and its 2-cyanomethyl derivative, respectively (66AP997).

Perhydroquinolines (**72**) were obtained in almost quantitative yield from perhydro[1,3]oxazino[3,4-*a*]quinolin-1-one (**71**) on reaction with lith-



ium dialkylcuprate in a mixture of diethyl ether and THF at -73°C [84-JCS(CC)597, 84TL3247; 86CPB2380]. Similar products (72) could be obtained in moderate yield from 71 by treatment with Zn in acetic acid (84TL3247), or from the perhydro derivative (73) by selenium(IV) oxide elimination and subsequent treatment with Zn in acetic acid at 90°C (80JA1454).

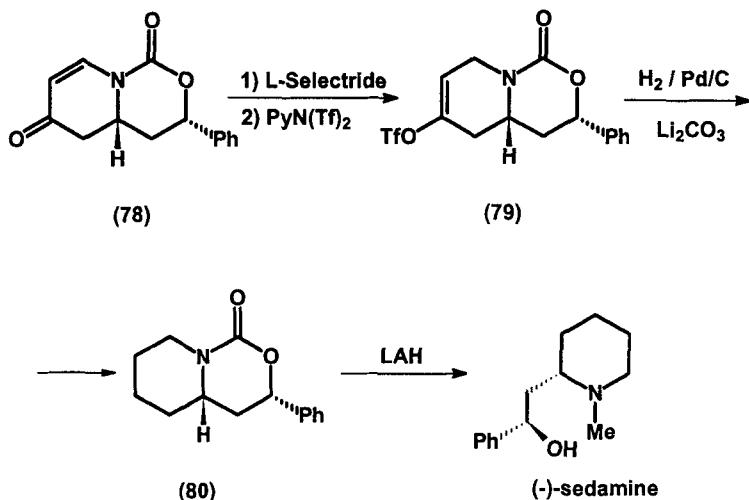


2-(Tetrahydroisoquinol-1-yl)ethanols (**74**) could be converted by inversion into the epimers (**77**) by *N*-benzoylation, subsequent treatment of **75** with thionyl chloride, and hydrolysis of the tricycles (**76**) (92T4937).

Reduction of a spiro compound, dodecahydro-3,3'-bi-1*H*,3*H*-pyrido[1,2-*c*][1,3]oxazine, with sodium amalgam in acetic acid led to reductive cleavage of one of the two tetrahydro[1,3]oxazine rings [71LA(753)27].

2. Reduction

Conjugate 1,4-reduction of the 1,6-dione (**78**) with *L*-Selectride in the presence of *N*-(2-pyridyl)triflimide provided the vinyl triflate (**79**), which was chemoselectively hydrogenated over Pd/C to give perhydropyrido[2,1-*c*][1,3]oxazinone (**80**) (93JOC5035). Hexahydro derivative **81** was similarly hydrogenated to a perhydro derivative (93JA8851).



Reduction of the keto group of the C(3) epimers of 3-phenylperhydropyrido[1,2-*c*][1,3]oxazin-6-ones with potassium trisamylborohydride in THF at -78°C gave a 9 : 1 mixture of the axial alcohol and the equatorial alcohol, whereas the ratio of the alcohols was the reverse when NaBH₄ was used in methanol at room temperature (85T2891).

Catalytic hydrogenation of *trans*-3,4*a*-H-3-methyl-1,3,4,4*a*,5,6-hexahydropyrido[1,2-*c*][1,3]oxazin-1-one over Pd/C afforded the perhydro derivative in excellent yield (91TL4371).

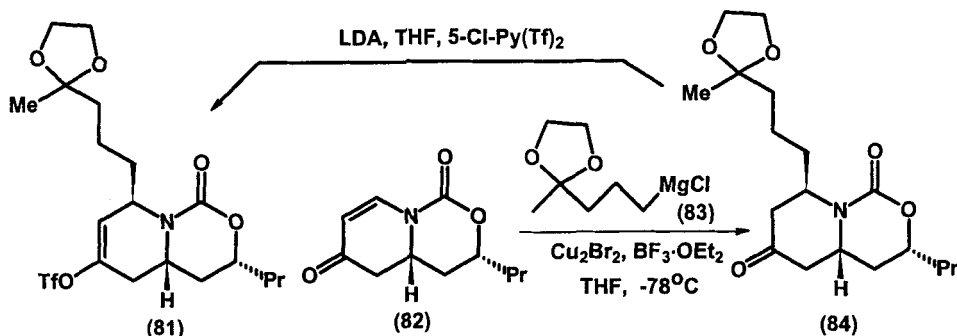
Catalytic hydrogenation of 1-cyano-9,10-dimethoxy-2,4,6,7-tetrahydro[1,3]oxazino[4,3-*a*]isoquinoline over Pd/C at atmospheric pressure in a suspension in ethyl acetate yielded the 1,2,4,6,7,11*b*-hexahydro derivative

(73JHC435). The 5,6 double bond of 1-isopropylidene-4,4-dimethyl-1,3,4,4*a*-tetrahydro[1,3]oxazino[3,4-*a*]quinolin-3-one (**67**, R = valence bond) was saturated on reaction with hydrogen over Pd/C [67JCS(C) 1569; 71JOC2211].

The 7-oxo group of 6,7-dihydro-1*H*,3*H*,5*H*-pyrido[3,2,1-*ij*][3,1]benzoxazine-3,7-dione was selectively reduced to a hydroxy group with sodium borohydride in methanol (87EUP239129; 90CPB1575).

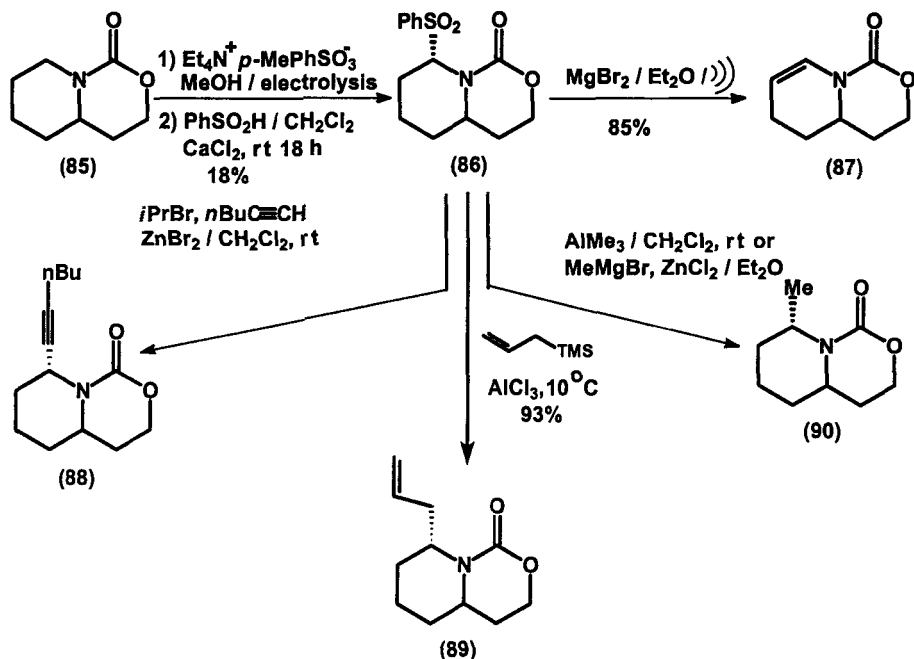
3. Reactivity of Rings

Methobromides (54JA2431) and methoiodides [60AP74; 63AP38; 70-LA(737)24] of perhydropyrido[1,2-*c*][1,3]oxazines were prepared from the bases with the respective methyl halides. The rates of quaternization of 4-methylperhydropyrido[1,2-*a*][1,3]oxazines (70T1217), three isomers of perhydropyrido[1,2-*c*][1,3]benzoxazines (**21–23**) (70T1217), and all isomeric perhydropyrido[3,2,1-*ij*][3,1]benzoxazines (**25–28**) [80JCS(P2)1778] with methyl iodide were measured in acetonitrile at 29–30°C.



Copper-mediated 1,4-addition of Grignard reagent (**83**) to hexahydro-pyrido[1,2-*c*][1,3]oxazine-1,6-dione (**82**) afforded perhydro derivatives (**84**) (93JA8851). Reaction of 1,6-dione (**84**) with LDA and N -(5-chloro-2-pyridyl)triflimide gave vinyltriflate (**81**), which contained 10% of the regioisomeric 1,3,4,4*a*,7,8-hexahydro derivative (93JA8851).

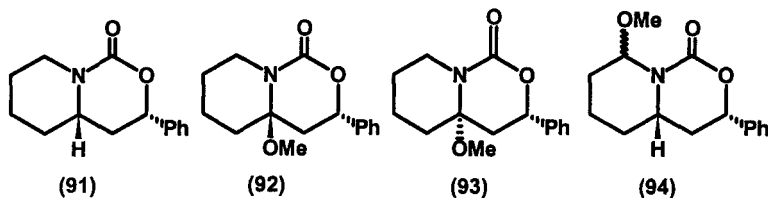
The 8-phenylsulfonyl derivative **86** was obtained when a solution of perhydropyrido[1,2-*c*][1,3]oxazin-1-one (**85**) and tetraethylammonium *p*-toluenesulfonate was electrolyzed and the evaporated residue was treated with benzenesulfinic acid and anhydrous calcium chloride (91T1311). From the 8-phenylsulfonyl derivative (**86**), the 7,8-unsaturated derivative (**87**) and different 8-substituted derivatives (**88–90**) could be prepared stereoselectively (90SL48, 90SL749; 91T1311) (see Scheme 13).



SCHEME 13

From the dimethyl acetal derivatives of perhydropyrido[1,2-*c*][1,3]oxazines (**33** and **34**), the phenylsulfonyl group was reductively removed with sodium amalgam to yield 5-unsubstituted derivatives (96SL100).

The treatment of methyl 1-oxo-1,3,4,4*a*,7,8-hexahydropyrido[1,2-*c*][1,3]oxazine-8-carboxylate with NaOMe in CH_3OD gave the 8-deuterated product (81JA7573).

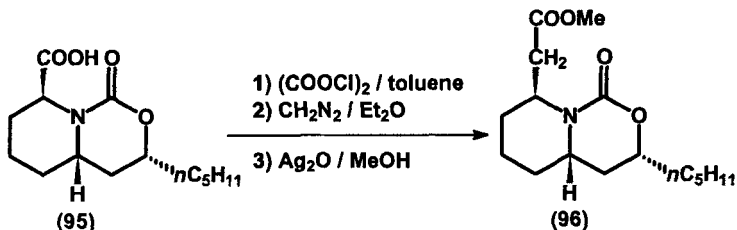


The anodic electrochemical oxidation of *cis*-3,4*a*-H-3-phenylperhydropyrido[1,2-*c*][1,3]oxazin-1-one (**91**) in methanol in the presence of tetraethylammonium *p*-toluenesulfonate gave a mixture of methoxylated pyrido[1,2-*c*][1,3]oxazin-1-ones (**92–94**) (91CJC211).

The 10-fluoro atom of 9,10-difluoro-7-oxo-1*H*,3*H*,7*H*-pyrido[3,2,1-*ij*][3,1]benzoxazine-6-carboxylic acids was regioselectively substituted by cyclic amines (90EUP373531; 96GEP4424369).

4. Reactivity of Substituents Attached to Ring Carbon Atoms

The carboxylic acid **95**, obtained from the methyl ester by alkaline hydrolysis, was converted by an Arndt–Eistert sequence to the higher homolog **96** (84JA3240). The ethyl esters of 7-oxo-1*H*,3*H*,7*H*-pyrido[3,2,1-*ij*][3,1]benzoxazine-6-carboxylates were hydrolyzed under basic conditions (90EUP373531). The carboxylic acid derivative was obtained by alkaline hydrolysis of methyl *trans*-4*a*,8-*H*-1-oxo-1,3,4,4*a*,7,8-hexahydropyrido[1,2-*c*][1,3]oxazine-8-carboxylate (81JA7573).



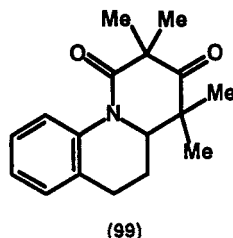
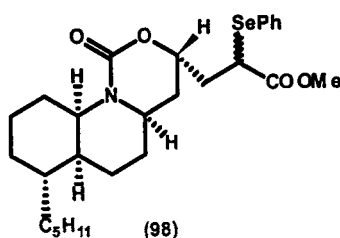
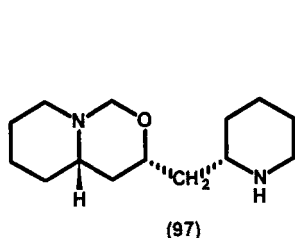
The carbonyl group in the side chain at position 8 of perhydropyrido[1,2-*c*][1,3]oxazines (**33**) and (**34**) was converted to the dimethylacetal on the treatment with triethyl orthoformate in methanol in the presence of *p*-toluenesulfonic acid (96SL100).

7-(*N*-Allylamino)-6,7-dihydro-1*H*,3*H*,5*H*-pyrido[3,2,1-*ij*][1,3]benzoxazin-3-one was *N*-methylated with formic acid–formaldehyde to furnish the 7-(*N*-allyl-*N*-methyl)amino derivative (87EUP239129; 90CPB1575). Treatment of 7-hydroxylimino-6,7-dihydro-1*H*,3*H*,5*H*-pyrido[3,2,1-*ij*][3,1]benzoxazin-3-one with a mixture of formic acid and formaldehyde at 100°C afforded the 7-dimethylamino derivative (87EUP239129).

The side-chain piperidine ring of **97** was *N*-acylated with benzoyl chloride and phenyl isocyanate [70LA(737)24], and the hydroxy group of compound (**38**, R = OH, R¹ = Me, R² = Ph) was acylated with benzoyl chloride (85GEP3439131; 90CB803). The HO → Cl exchange did not occur when **44** was boiled in SOCl₂ (90T4039).

Oxidative elimination of the phenylselenyl group of the perhydro[1,3]oxazino[3,4-*a*]isoquinoline (**98**) was effected with 30% H₂O₂ in the presence of pyridine to afford **71** in quantitative yield [84JCS(CC)597; 86CPB2380].

4-(2-Piperidylmethyl)perhydropyrido[1,2-*c*][1,3]oxazines were reacted with phenyl isothiocyanate and benzoyl chloride [70LA(737)24].



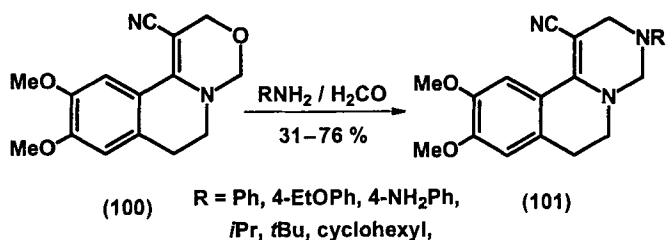
4-(Phenylimino)-1-hydroxymethyl-9,10-dimethoxy-1,2,4,6,7,11*b*-hexahydro[1,3]oxazino[4,3-*a*]isoquinoline was prepared from 4-methylimino and 4-thione derivatives in the presence of HgO and 4-methylthio-1,6,7,11*b*-tetrahydro-2*H*-[1,3]oxazino[4,3-*a*]isoquinolinium salt with aniline (85GEP3510526). 4-Methylthio-1-hydroxymethyl-9,10-dimethoxy-1,6,7,11*b*-tetrahydro-2*H*-[1,3]oxazino[4,3-*a*]isoquinolinium iodide was obtained from the 1,2,4,6,7,11*b*-hexahydro-4-thione derivative with methyl iodide (85GEP3510526). 1-Hydroxymethyl-9,10-dimethoxy-1,2,4,6,7,11*b*-hexahydro-[1,3]oxazino[4,3-*a*]isoquinolin-4-thione was obtained from its 4-one derivative by treatment with P₄S₁₀ in pyridine (85GEP3510526).

The 7-hydroxy group of 7-hydroxy-6,7-dihydro-1*H*,3*H*,5*H*-pyrido[3,2,1-*ij*][3,1]benzoxazin-3-one was alkylated with alkyl halide in DMSO in the presence of sodium hydride (87EUP239129; 90CPB1575). The 7-oxo group of 3,4,5,6-tetrahydro-1*H*-pyrido[3,2,1-*ij*][3,1]benzoxazine-3,7-dione was converted into the 7,7-ethylenedioxy group by treatment with ethylene glycol in the presence of *p*-toluenesulfonic acid in boiling toluene. It was then condensed with hydroxylamine hydrochloride in the presence of sodium acetate and with allylamine in the presence of *p*-toluenesulfonic acid and molecular sieve 3Å, and the imine was reduced with NaBH₄ to give the 7-allylamine derivative (87EUP239129; 90CPB1575).

5. Ring Transformation

2-Aryl-1,6,7,8,9,9*a*-hexahydro-4*H*-quinolizines were obtained when 3-aryl-methylperhydropyrido[1,2-*c*][1,3]oxazine hydrochlorides were heated in concentrated hydrochloric acid (60BRP856357; 62USP3031454).

Ethyl 4,5,6,7,8,8*a*-hexahydro-3*H*-quinolizine-1-carboxylate was obtained in 82% yield from 1-oxo-3-vinylperhydropyrido[1,2-*c*][1,3]oxazine-4-carboxylate on the action of DBU in DMSO [88CPB1597; 90H(30)885]. Rearrangement of [1,3]oxazino[3,4-*a*]quinoline (**67**, R = H) in the presence of NaOMe in cyclohexane at 65°C produced benzo(*c*)quinolizine-1,3-dione (**99**) (71JOC2211).



Treatment of 1-cyano-9,10-dimethoxy-2,4,6,7-tetrahydro[1,3]oxazino[4,3-*a*]isoquinoline (**100**) with primary amine and aqueous formaldehyde in boiling ethanol afforded 2-substituted 1-cyano-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolines (**101**) (73JHC435).

Different di-, tri-, tetra-, and pentacyclic heterocycles were prepared from 6,7-dihydro-1*H*,3*H*,5*H*-pyrido[3,2,1-*ij*][3,1]benzoxazine (**102**) as depicted in Scheme 14 (78JHC645; 79JHC829; 80JHC1785; 83EUP59698; 84MIP1).

See further examples in Section IV,B,6.

6. Miscellaneous

The epimers of *cis*-3,4*a*-H-3-phenylperhydropyrido[1,2-*c*][1,3]oxazin-6-one were separated with camphor-10-sulfonic acid in acetone (85T2891). The enantiomers of 6,10,11,11*a*-tetrahydropyrido[1,2-*c*][1,3]benzoxazin-6-one were quantitatively separated by means of HPLC on swollen microcrystalline triacetylcellulose with ethanol-water (96:4) as the mobile phase. The first-eluted enantiomer had the *R* configuration (91ACS716).

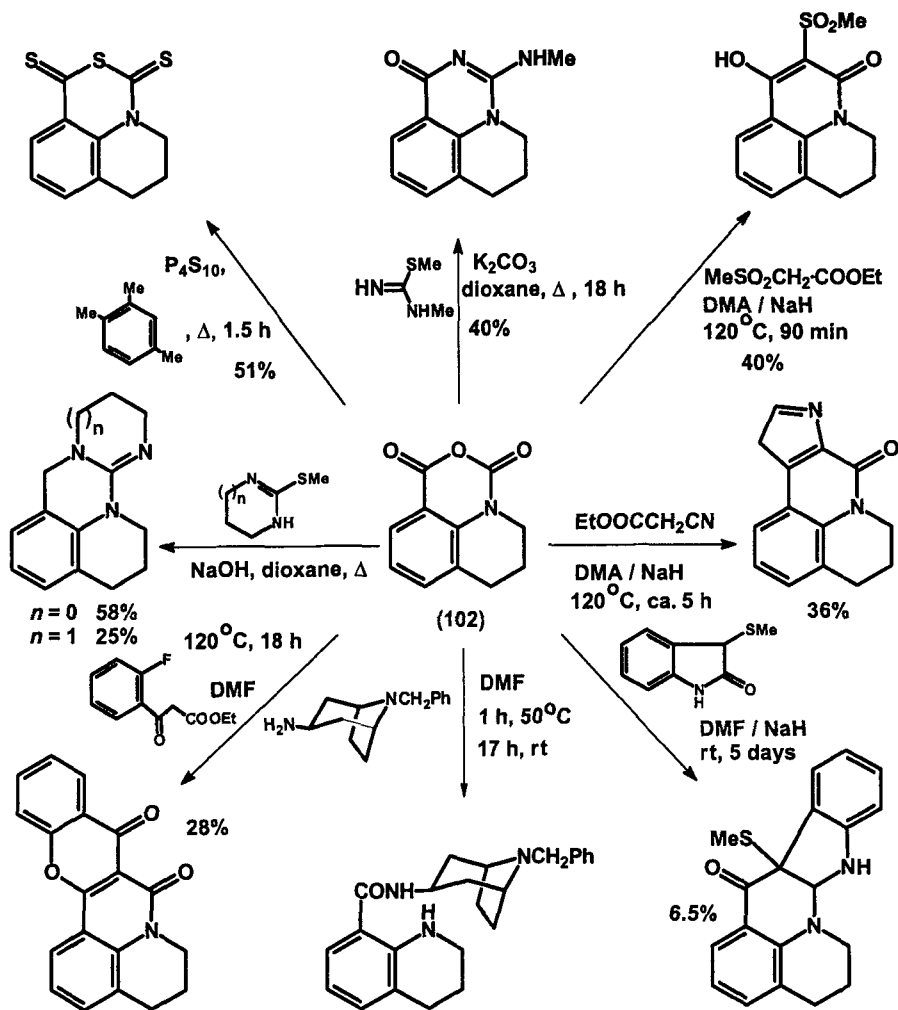
The electrochemical reduction of 1-hydroxymethyl-9,10-dimethoxy-4-cyclohexylimino-1,2,4,5,6,11*b*-hexahydro[1,3]oxazino[4,3-*a*]isoquinoline on a dropping Hg electrode was studied (87PHA858).

B. PYRIDO[1,2-*c*][1,3]THIAZINES AND THEIR BENZO DERIVATIVES

1. Ring Opening

Reductive desulfurization of all-*cis*-3,4*a*,5,6-H-3-phenyl-5-substituted 6-formylperhydropyrido[1,2-*c*][1,3]thiazin-1-ones with Raney Ni in boiling ethanol gave all-*cis*-2,3,4-H-1-formyl-2-(2-phenethyl)-3-substituted piperidin-4-ols (85T2861).

Reaction of 1-iminoperhydropyrido[1,2-*c*][1,3]thiazine hydrobromides with tetraethylenepentamine in boiling ethanol afforded 2-(2-mercaptoethyl)piperidines [70T3941; 82OMR(20)239].



SCHEME 14

2. Reactivity of Rings

The reaction of 1,3,4,4a,5,10-hexahydro[1,3]thiazino[3,4-b]isoquinoline-1-thione and methyl iodide gave 1-methylthio-4,4a,5,10-tetrahydro-3H-[1,3]thiazino[3,4-b]isoquinolinium iodide, which reacted with 5-aminoisoquinoline in pyridine at $40^\circ C$ to afford 1-(5-isoquinolyylimino)-1,3,4,4a,5,10-hexahydro[1,3]thiazino[3,4-b]isoquinoline (79GEP2848926).

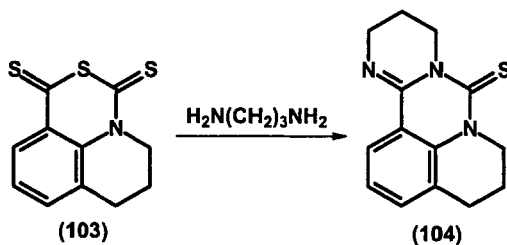
The 4-(substituted imino) moiety of 1,2,4,6,7,11*b*-hexahydro-2*H*-[1,3]thiazino[4,3-*a*]isoquinolines was substituted with another (substituted imino) group when 9,10-dimethoxy-1-hydroxymethyl-4-(substituted imino)-1,2,4,6,7,11*b*-hexahydro-[1,3]thiazino[4,3-*a*]isoquinolines were reacted with primary amines in boiling ethanol (85GEP3510526).

3. Reactivity of Substituents Attached to Ring Carbon Atoms

trans-1,11*b*-*H*-1-Benzoyloxymethyl-9,10-dimethoxy-4-phenylimino-1,2,3,6,7,11*b*-hexahydro[1,3]thiazino[4,3-*a*]isoquinoline was obtained from the 1-hydroxymethyl derivative by reaction with benzoyl chloride in boiling pyridine (90CB803).

4. Ring Transformation

The reaction of 6,7-dihydro-1*H*,3*H*,5*H*-pyrido[3,2,1-*ij*][3,1]benzothiazine-1,3-dithione (**103**) with 1,3-diaminopropane afforded the tetracyclic compound (**104**) (78JHC645).



5. Miscellaneous

The electrochemical reduction of 4-(substituted imino)-1,2,4,5,6,11*b*-hexahydro[1,3]thiazino[4,3-*a*]isoquinolines on a dropping Hg electrode was studied in the pH range 1–11 (87PHA858).

C. PYRIDO[1,2-*c*]PYRIMIDINES AND THEIR BENZO DERIVATIVES

1. Ring Opening

2-(1-Aminocarbonyl-2-piperidyl)acetic acid was obtained from perhydropyrido[1,2-*c*]pyrimidine-1,3-dione by reaction with 30% aqueous KOH at 60–70°C (56CB1642). Treatment of 1,3-dimethyl-5,6,7,8-tetrahydropyr-

ido[1,2-*c*]pyrimidinium-4-carboxylate with aqueous ammonia gave 4-(4-ammoniobutyl)-2,6-dimethylpyrimidine-5-carboxylate (87JOC2455). Basic hydrolysis of 4-cyano-5,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*]pyrimidin-3-one led to a ring-opened product (82KGS518).

Treatment of 9,10-dimethoxy-1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-2,4-dione with LAH in dioxane at 80°C yielded ring-opened 2-(2-methylaminoethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (59-YZ1008). Heating 9,10-dimethoxy-1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinoline or its 3-methyl derivative in a mixture of 35% formaldehyde and 80% formic acid gave 1-dimethylamino-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (59YZ1008). Heating 9,10-dimethoxy-6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinolin-2-one in a sodium hydroxide solution gave 1-aminocarbonylmethylene-1,2,3,4-tetrahydroisoquinoline [81KFZ(5)44; 82KGS1095]. Acidic hydrolysis of 9,10-dimethoxy-4-phenyl-1,6,7,11*b*-tetrahydro- and 1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines (84JHC149) and 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrimido[1,6-*a*]quinoline (60YZ1414) led to ring-opened products. 1-[(Acylamidino)methylene]-6,7-dialkoxy-1,2,3,4-tetrahydroisoquinolines (**48**) were obtained when 2-imino-4-substituted 9,10-dialkoxy-6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinoline hydrochlorides were treated with aqueous potassium hydroxide or their hydrates (**51** · H₂O) were left to stand in ethanol overnight (90CB493).

Reduction of 9,10-dimethoxy-1-(un)substituted 3-substituted 1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolones with NaBH₄ in acetic acid afforded ring-opened 6,7-dimethoxy-2-methyl-1-[2-(substituted amino)-2-oxo]ethyl-1,2,3,4-tetrahydroisoquinolines (92GEP4104257).

See further examples in Section III,C,4.

2. Reduction, Hydrogenation

Perhydropyrido[1,2-*c*]pyrimidine was obtained from perhydropyrido[1,2-*c*]pyrimidine-1,3-dione (59CB637) and from perhydropyrido[1,2-*c*]pyrimidin-1-one [67YZ663; 73OMR(5)397] by reduction with LAH. Reduction of 2-oxo- and 2,4-dioxo-1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines and 1-oxo-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrimido[1,6-*a*]quinoline with LAH gave hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines [59YZ1008; 77JCS(P2)370] and hexahydro-1*H*-pyrimido[1,6-*a*]quinoline (60YZ1414), respectively.

Reduction of 2-benzyl-1,2,3,5,6,7-hexahydropyrido[3,2,1-*ij*]quinazolin-7-one with NaBH₄ and hydrazine hydrate in the presence of KOH gave 7-hydroxy and 7-deoxy derivatives, respectively (72MI1).

Catalytic reduction of 1-cyano-6,7-dihydro- and 1-cyano-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolines or of 1-cyano-3-acetoxy-

1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinoline over Pd/C gave 1-cyano-1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines (81CB61; 84MI3). Catalytic reduction of 4-(*p*-nitrophenyl)-9,10-dimethoxy-6,7-dihydro-2*H*-pyrido[6,1-*a*]isoquinoline over PtO₂ in acidic methanol gave 4-(*p*-aminophenyl)-6,7-dihydro and 4-(*p*-aminophenyl)-1,3,4,6,7,11*b*-hexahydro derivatives after the absorption of 3 and 5 mol hydrogen, respectively (55JPJ709, 55MI2). 9,10-Dimethoxy-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-one was prepared from 6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-one and its 2-chloro derivative by catalytic hydrogenation over Pd/C (84JMC1470).

Catalytic reduction of 4-benzyl-2-phenyl-2,3-dihydro-1*H*-pyrimido[6,1-*a*]quinoline-1,3-dione with hydrogen over 5% Pt/C in acetic acid at 50°C for 15 h gave the 2,3,5,6,6*a*,7,8,9,10,10*a*-decahydro-1*H* derivative (83M227).

Treatment of 2-substituted 4-cyano-3-imino-2,3,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidin-1-ones with NaBH₄ in ethanol gave 3-amino-2,4*a*,5,6,7,8-hexahydro-1*H* derivatives (90MI3). The N(3)-C(4) double bond of 6,7-dihydro- and 1,6,7,11*b*-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolines was saturated by treatment with NaBH₄ (81CB61; 84JHC149, 84MI3). Electrochemical reduction of 4-aryl-9,10-dialkoxy-1,6,7,11*b*-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-2-ones afforded the 1,3,4,6,7,11*b*-hexahydro derivatives (87PHA739; 89PHA694). Reduction of 9,10-dimethoxy-2,3,6,7-tetrahydro-4*H*-pyrimido[6,1-*a*]isoquinoline-2,4-dione with Mg in methanol yielded the 1,2,3,6,7,11*b*-hexahydro derivative (90JOC5117). 2-Amino-9,10-dimethoxy-4-phenyl-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinoline was obtained when 2-imino-9,10-dimethoxy-4-phenyl-6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinoline was hydrogenated over Pd/C (90CB493).

3. Reactivity of Ring Nitrogen Atoms

The 2-methyl derivative was prepared from perhydropyrido[1,2-*c*]pyrimidine-1,3-dione on treatment with diazomethane in aqueous methanol (56CB1642). The methiodide was obtained from perhydropyrido[1,2-*c*]pyrimidine with methyl iodide (59CB637).

The nonbridgehead nitrogen of perhydropyrido[1,2-*c*]pyrimidines (69JHC181) and their 3-oxo (84EUP104647; 85JMC1285) and 1,3-dioxo derivatives (64JMC146; 87USP4680295) and 2,3-dihydro-1*H*-pyrido[1,2-*c*]pyrimidine-1,3-diones (57HCA1319), and that of 9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*- (77SAP77/06706; 78GEP2720085; 79GEP2801289; 80GEP2847693; 84JMC1470), 1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-2,4-diones (69YZ649; 84T4003; 90JOC5117), as well as that of 2,3,4,4*a*,5,6-1*H*-pyrimido[1,6-*a*]quinolin-1-ones (70USP3494922), has been alkylated, and the nonbridgehead nitrogen of perhydropyrido

[1,2-*c*]pyrimidine [73OMR(5)397], its 1-oxo derivative (90MIP1), its 1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinoline (59YZ1008), and its 2,4-dione derivative has been acylated (84T4003).

The alkylation of 2-(substituted amino)-9,10-dimethoxy-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-ones usually led to a mixture of 2-(disubstituted amino)-6,7-dihydro and 2-(substituted imino)-3-alkyl-2,3,6,7-tetrahydro derivatives (e.g., **54** and **53**) (81INIP149457; 84EUP124893, 84JMC1470; 86HCA1671). The ratio of the 3-alkyl-2,3,6,7-tetrahydro and the 2-(disubstituted amino)-6,7-dihydro derivatives varied and depended on the size of the alkyl group and the alkylation conditions (84JMC1470). The ratio of the 3-alkyl-2,3,6,7-tetrahydro isomers was higher when K₂CO₃/acetone was used instead of NaH/DMF, and the ratio decreased with increasing alkyl group. (Earlier the starting compounds were described as 4-[substituted amino]-2-oxo derivatives [79GEP2801289].

Hydrolysis of 2-acetyl-1-[cyano(nitro)methylene]perhydropyrido[1,2-*c*]pyrimidine in boiling 5 *N* hydrochloric acid gave the 2-unsubstituted derivative [74JCS(P)1611].

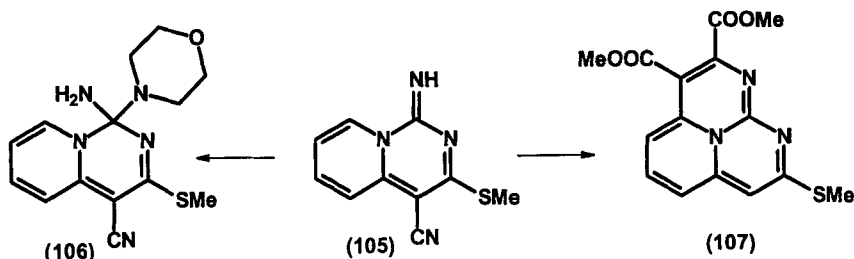
4. Reactivity of Ring Carbon Atoms

Treatment of 4-phenyl-2,3-dihydro-1*H*-pyrido[1,2-*c*]pyrimidine-1,3-dione with POCl₃ in the presence of *N,N*-dimethylaniline gave 3-chloro-4-phenyl-1*H*-pyrido[1,2-*c*]pyrimidin-1-one. The 3-chloro atom could be substituted by amino and alkoxy groups. Treatment of the 3-chloro derivative with thiourea afforded 4-phenyl-3-thioxo-2,3-dihydro-1*H*-pyrido[1,2-*c*]pyrimidin-1-one (57HCA1319).

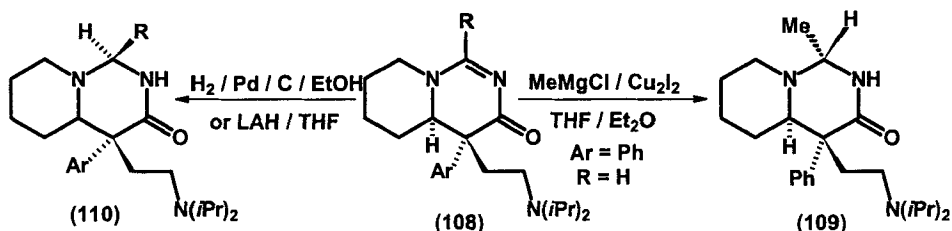
Treatment of 9,10-dimethoxy-6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinolin-2-ones with POCl₃ gave 2-chloro-6,7-dihydropyrido[6,1-*a*]isoquinolinium chlorides, which were subsequently reacted with an amine or hydrazide to give 2-(substituted amino)-6,7-dihydropyrimido[6,1-*a*]isoquinolinium chlorides (82KGS1095). Heating 9,10-dimethoxy-2,3,6,7-tetrahydro-4*H*-pyrimido[6,1-*a*]isoquinoline-2,4-diones in POCl₃ gave 2-chloro-6,7-dihydro-4-one derivatives [81FRP2470130; 84JMC1470, 84USP4482556; 89H(29)1929]. (Earlier the products were described as 4-chloro-2-oxo derivatives [77SAP77/06706; 78GEP2720085]). The chlorine atom in 2-chloro-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-ones was substituted with amines [80GEP2847693, 80INIP147624; 81FRP2470130; 84EUP124893, 84USP4482556; 86HCA1671; 89H(29)1929] or with sodium butoxide and phenoxide (84JMC1470), or was hydrolyzed with water [89H(29)1929]. Treatment of 2-methylthio-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-ones with amines yielded 2-(substituted amino) derivatives (84JMC1470). (Earlier the starting compounds were described as 4-methylthio-2-oxo de-

rivatives [77SAP77/06706; 78GEP2720085; 79GEP2801289]). Reaction of 2-chloro-3-methyl-9,10-dimethoxy-4-oxo-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolinium chloride with mesitylene gave the 2-[(2,4,6-trimethylphenyl)imino]2,3,6,7-tetrahydro-4*H* derivative (85GEP3340773).

2-Benzyl-1,2,3,5,6,7-hexahydropyrido[3,2,1-*ij*]quinazolin-7-one was acylated at position 9 by heating in acetic acid (72MI1).

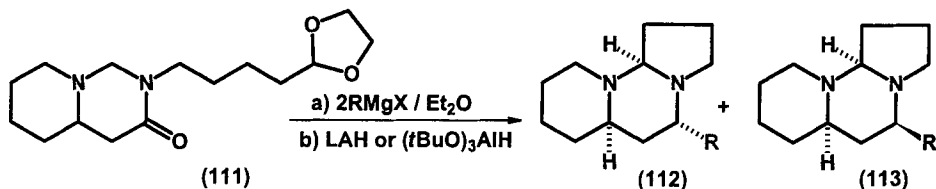


Treatment of 1-imino-4-cyano-3-methylthio-1*H*-pyrido[1,2-*c*]pyrimidine (**105**) with morpholine afforded the 1-amino-1-morpholine derivative (**106**). Reaction of the 1-imino derivative (**105**) with dimethyl acetylenedicarboxylate gave the diaza[3,3,3]azine derivative (**107**) (75YZ13). Treatment of **105** with concentrated H_2SO_4 or with acetic acid yielded 4-aminocarbonyl-3-methylthio-1*H*-pyrido[1,2-*c*]pyrimidin-1-one and 4-cyano-3-methylthio-1*H*-pyrido[1,2-*c*]pyrimidin-1-one, respectively. Reaction of the latter derivative with morpholine afforded the 3-morpholino derivative (75YZ13). Hydrolysis of 4-cyano-3-imino-2,3,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidine-1-(thi)ones or their 3-(aminocarbonyl)imino derivatives in boiling 70% HCl gave 3-oxo derivatives (78MI1).



Methylation of 4,4*a*,5,6,7,8-hexahydro-3*H*-pyrido[1,2-*c*]pyrimidin-3-one (**108**, $\text{R} = \text{H}$) with methylmagnesium chloride in the presence of Cu_2I_2 or Cu_2Br_2 gave 1-methylperhydropyrido[1,2-*c*]pyrimidin-3-one (**109**) (84EUP104647; 85JMC1285). Reduction of **108** either over Pd/C

under hydrogen or with LAH gave perhydropyrido[1,2-*c*]pyrimidin-3-ones (**110**).



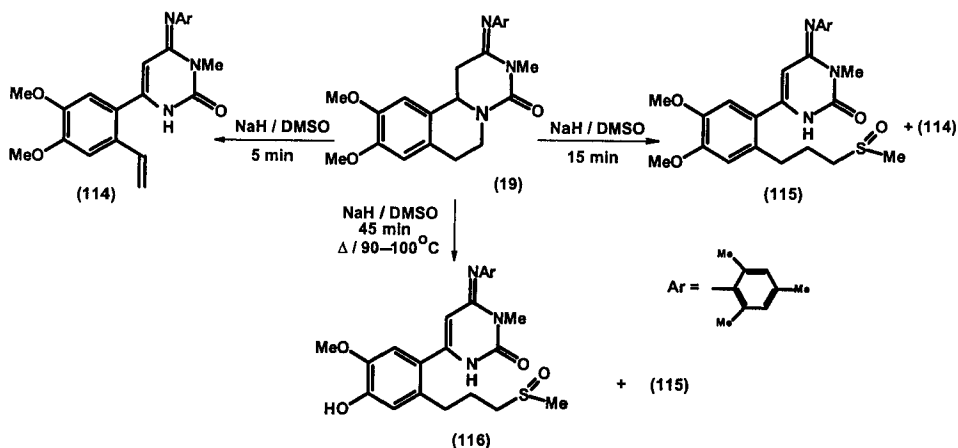
Reaction of perhydropyrido[1,2-*c*]pyrimidin-3-one (**111**) with 2 equiv propylmagnesium chloride, and subsequent treatment of the reaction mixture with LAH, gave 30% of a 1:3 mixture of tricycles (**112**, R = *n*Pr) with the unsubstituted tricycle (**112**, R = H). When lithium tri-*tert*-butoxyaluminumhydride was used in the reduction step, (±)-tetraponerine-T4 alkaloid (**113**, R = *n*Pr) was obtained, containing less than 5% of **112** (R = *n*Pr). The addition of 1 equiv tetramethylethylenediamine increased the overall yield of **113** (R = *n*Pr) to 70%, with less than 1% of **112** (R = *n*Pr). Tetraponerine-T8 (**113**, R = C₅H₁₁) was prepared similarly by using pentylmagnesium bromide (90TL4543).

Treatment of 2,4,4-trimethyl-5-phenyl-1-thioxo-3-oxo-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidine with Lawesson's reagent gave a 1,3-dithioxo derivative [96H(42)117]. Treatment of a 4-thioxo-1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-2-one derivative with Hg(OAc)₂ in boiling acetic acid gave the 2,4-dioxo derivative, and with Raney Ni in boiling ethanol yielded the 2-oxo derivative (69YZ649). In the latter case the 3-(4-bromophenyl) group was converted into a 3-phenyl group. 9,10-Dimethoxy-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-one was obtained from its 2-methylthio derivative by reaction with Raney Ni in boiling acetone (84JMC1470).

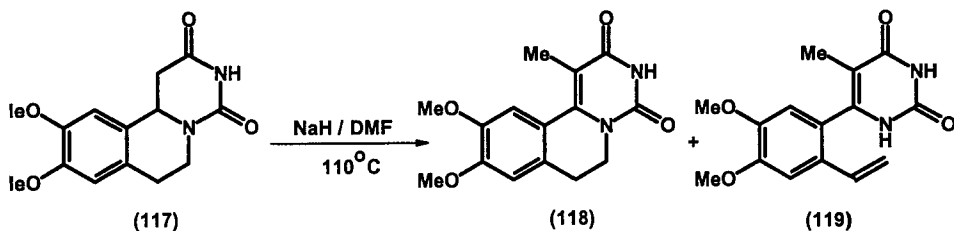
Heating 3-acetoxy-1-cyano-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline yielded the 6,7-dihydro derivative by elimination of acetic acid (81CB61; 84MI3).

Reaction of 9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-2,4-diones (84JMC1470) and 2-[2-(1-pyrrolidiny)ethyl]-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrimido[1,6-*a*]quinolin-1-one (70USP3494922) with P₄S₁₀ gave the 2-thioxo and 1-thioxo derivatives, respectively. (In the first case the products were earlier described as 2-oxo-4-thioxo derivatives [77SAP77/06706; 78GEP2720085; 79GEP2801289].

Treatment of trequinsin (**19**) with dimsyl ion gave the ring-opened product **114** when a short reaction period (5 min) was applied, but a longer reaction period led to a mixture of **115** and **114** (reaction period 15 min), or a mixture of **116** and **115** (reaction period 45 min) (90JOC5117). Similar



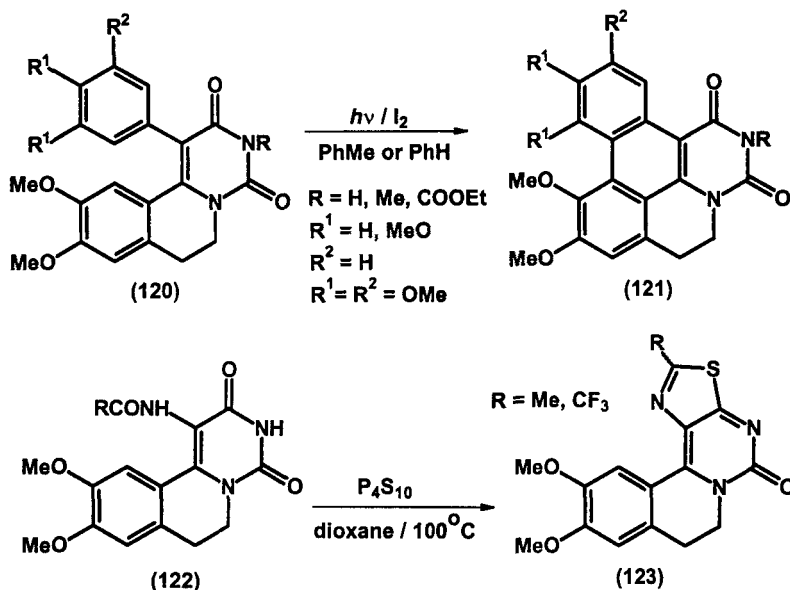
ring opening occurred when other 2-amino-6,7-dihydro-, 2-imino-, or 2-oxo-2,3,6,7-tetrahydro-4*H*-pyrido[6,1-*a*]isoquinolin-4-ones were treated with NaH (90JOC5117), or when 2-imino-6,7-dihydro-2*H*-pyrido[6,1-*a*]isoquinolines or their hydrated derivatives were heated (91CB111). Ring opening did not occur with 9,10-dimethoxy-1,2,3,5,6,11*b*-hexahydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-one (90JOC5117).



Treatment of 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrimido[6,1-*a*]isoquinoline-2,4-dione (117) with excess NaH in DMF yielded a mixture of the 1-methyl-2,3,6,7-tetrahydro and ring-opened compounds 118 and 119 (90JOC5117).

Heating 4-benzyl-2-phenyl-2,3-dihydro-1*H*-pyrimido[1,6-*a*]quinoline-1,3-dione in the presence of AlCl₃ at 180°C for 30 min yielded a 4-debenzyl derivative (83M227). Reaction of 2-phenyl-2,3-dihydro-1*H*-pyrimido[1,6-*a*]quinoline-1,3-dione with sulfuryl chloride in dioxane at 50–60°C for 2 h, then at 70°C, gave 2-phenyl-4,4,4*a*-trichloro-2,3,4,4*a*-tetrahydro-1*H*-pyrimido[1,6-*a*]quinoline-1,3-dione (83M227).

The photocyclization of 1-aryl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-2,4-diones (120) to pyrimidoaporphine derivatives (121) has been studied (84T4003). Reaction of 1-acylamido-2,3,6,7-tetrahydro-4*H*-



pyrimido[6,1-*a*]isoquinoline-2,4-diones (**122**) with P_4S_{10} gave thiazolo[5,4-*b*]pyrimido[6,1-*a*]isoquinolin-5-ones (**123**) [89H(29)1929].

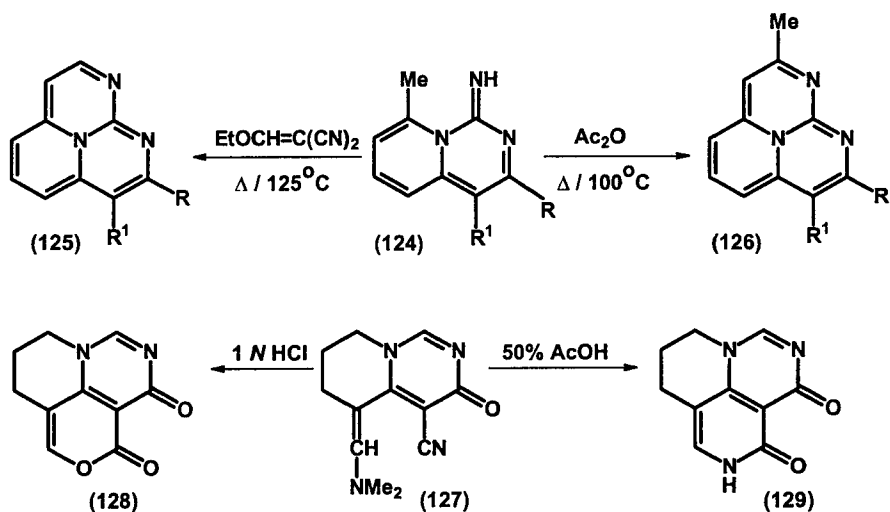
Oxidation of 1-aryl-9-methoxy-1,2,3,5,6,7-hexahydro-7*H*-pyrido[3,2,1-*ij*]-quinazolin-3-ones with $KMnO_4$ in dioxane gave 1,2,3,7-tetrahydro derivatives (73USP3709887).

5. Reactivity of Substituents Attached to Ring Carbon Atoms

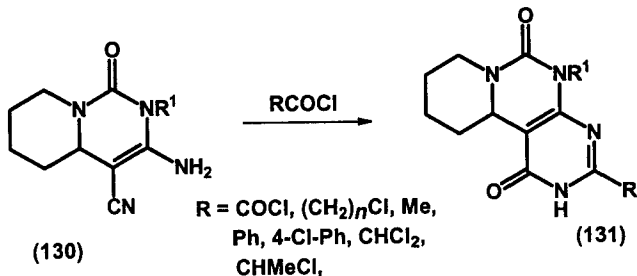
Methylthio derivatives were prepared from perhydropyrido[1,2-*c*]pyrimidine-1-thiones (62JOC1970; 71JMC878; 72USP3631046; 74USP3772230; 75USP3868372) and from 9,10-dimethoxy-2-thioxo-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-ones (84JMC1470) with methylating agents. (In the case of the pyrimido[6,1-*a*]isoquinoline derivative, the starting compounds were earlier described as 4-thioxo-2-oxo derivatives [77SAP77/06706; 78GEP2720085; 79GEP2801289].

1,9-Diazacycl[3,3,3]azines (**125** and **126**) were prepared by the reaction of 1-imino-8-methyl-1*H*-pyrido[1,2-*c*]pyrimidines (**124**) with ethoxymethylenemalononitrile and acetic anhydride, respectively (74CPB2765; 78YZ623). In the latter cases, the hydrolysis of the imino group also occurred to give 4-oxo derivatives of **124** (78YZ623).

Heating pyrido[1,2-*c*]pyrimidin-3-one (**127**) in 1 *N* HCl or in 50% acetic acid afforded the tricyclic derivatives **128** and **129**, respectively (82KGS518).



Treatment of 2-substituted 3-amino-4-cyano-2,4*a*,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidin-1-ones (130) with acyl chlorides afforded tricyclic 3,5-disubstituted 2,5,6,8,9,10,11,11*a*-octahydro-1*H*-pyrido[1,2-*c*]pyrimido[5,4-*e*]pyrimidine-1,6-diones (131) (90MI3; 93MI1, 93MI3).



The 3-imino group of 4-cyano-2-ethyl-3-imino-2,3,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidine-1-thione was acylated with phenyl isocyanate (78MI1). The imino group of 1-imino-4-cyano-3-methylthio-1*H*-pyrido[1,2-*c*]pyrimidine was alkylated and acylated with methyl iodide and acetic anhydride (75YZ13). Reaction of 3-amino-4-phenyl-4-[2-(*N,N*-di-*n*-propylamino)ethyl]-4*a*,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidin-1-one with acetic anhydride in pyridine and with sodium nitrite in aqueous acetic acid afforded 3-acetamido and perhydro-1,3-dioxo derivatives, respectively (87USP4680295).

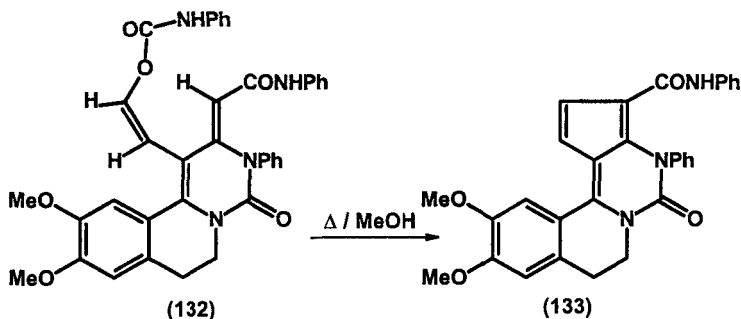
The hydroxy groups of 9-methoxy-10-hydroxy- and 9-hydroxy-10-methoxy-3-methyl-2-(*N*-methylimino)-2,3,6,7-tetrahydro-4*H*-pyrimido[6,1-

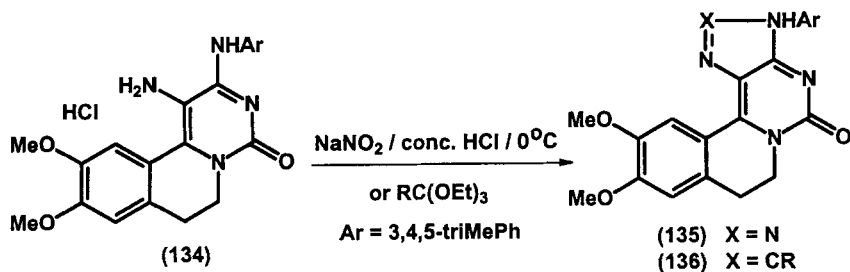
a]isoquinolin-4-ones were alkylated with epibromohydrin to give 3'-bromo-2'-hydroxypropyl (84INIP153028) or 2',3'-epoxypropoxy derivatives (83EUP75165). The epoxy and bromo derivatives were reacted with amines (83EUP75165; 84INIP153028). The side-chain hydroxy group of 3-(2-hydroxyethyl)-9,10-dimethoxy-1,3,4,5,6,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-2-one was acylated with acyl chlorides (61JMC505; 62USP3021331). The hydroxy group of 3-hydroxy-3,4,6,7-tetrahydro- and 1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines has been acetylated (81CB61). The side-chain benzylamino group of 2-substituted 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrimido[1,6-*a*]quinolin-1-ones was debenzylated by hydrogenation over Pd/C (70USP3494922).

Diazotization of 4-(*p*-aminophenyl)-9,10-dimethoxy-6,7-dihydro- and -1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines, followed by treatment with 30% H₃PO₂, gave deaminated products (55CPB259).

Oxidation of the 4-methyl group on the phenyl ring of 9,10-dimethoxy-2-(2,4,6-trimethylphenylimino)-3-methyl-2,3,6,7-tetrahydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-one with DDQ gave a complex, which was treated with ZnCl₂ in boiling methanol to yield the 4-methoxymethyl derivative (84TL2901; 86INIP157279). The 4-methoxymethyl group was cleaved in 2 *N* hydrochloric acid to the hydroxymethyl group, which was oxidized with pyridinium chromate to the 4-aldehyde. The aldehyde was converted to its 4-oxime, which was dehydrated in refluxing Ac₂O, and the 4-nitrile was hydrolyzed with aqueous NaOH to give the 4-carboxy derivative (86INIP157279).

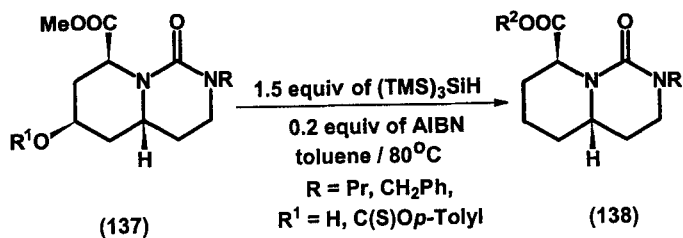
Heating pyrimido[6,1-*a*]isoquinolin-4-one (**132**) in methanol gave the tetracyclic compound **133** (86CB2553). The reaction of 1-amino-2-[(2,3,4-trimethylphenyl)amino]-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-one hydrochloride (**134**) with HNO₂ or with triethyl orthoesters gave the tetracyclic compounds **135** and **136**, respectively [89H(29)1929].





Acylation of 2-[(2,4,6-trimethylphenyl)amino]-9,10-dimethoxy-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-one with acetyl chloride gave a 2-acetamido derivative (84JMC1470). (Earlier the starting compound was described as a 4-amino-2-oxo-2*H* derivative, which afforded a mixture of 3-acetyl-4-[substituted imino]-2,3,6,7-tetrahydro-2-oxo-2*H* and 4-acetamido-6,7-dihydro-2-oxo-2*H* derivatives [77SAP77/06706; 78GEP2720085].

The acetamido group of 2-acetamido-1-[nitro(cyano)methylene]perhydropyrido[1,2-*c*]pyrimidine [74JCS(P1)1611], or that of 1-acetamido-2-(substituted amino)-6,7-dihydro- and 1-acetamido-2-oxo-2,3,6,7-tetrahydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-ones [89H(29)1929], was hydrolyzed by treatment with conc. HCl. In the latter case, the amino group was acylated with trifluoroacetyl anhydride.



The hydroxy group in **137** ($\text{R}^1 = \text{H}$) was acylated with *O-p*-tolyl chlorothionoformate (96JMC1872). The ester group of **138** ($\text{R}^2 = \text{Me}$) was hydrolyzed under basic conditions, and the carboxyl group was esterified with benzyl alcohol to give **138** ($\text{R}^2 = \text{CH}_2\text{Ph}$). The 6-thionoformate group of **137** ($\text{R}^1 = \text{C(S)O-p-Tolyl}$) was reduced to give 6-unsubstituted bicycles **138** (96JMC1872).

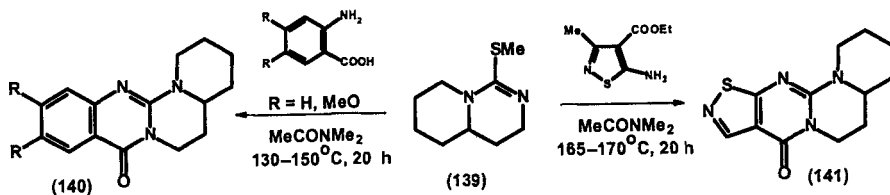
The reaction of 2-cyanomethylperhydropyrimidine with LAH gave the 2-(2-aminoethyl) derivative (69JHC181).

6. Ring Transformation

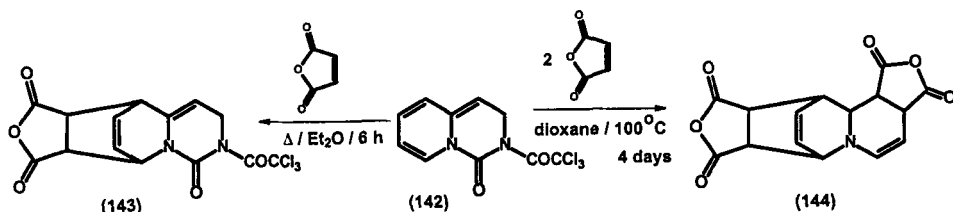
8-Cyano-1,2,3,4-tetrahydro-6*H*,7*H*-1,6-naphthyridin-7-one was obtained from **127** in boiling water (80KGS416, 80KGS1120) or by heating in DMF in the presence of benzylamine (82KGS518). Treatment of 2-benzyl-9-chloro-1,2,3,5,6,7-hexahydropyrido[3,2,1-*ij*]quinazolin-7-one with NaN_3 in chloroform in the presence of concentrated H_2SO_4 gave 2-benzyl-10-chloro-1,2,3,5,6,7-hexahydro-8*H*-pyrimido[5,6,1-*jk*][1,4]benzodiazepin-8-one (72MI1).

7. Miscellaneous

Cyclocondensation of 1-methylthio-4,4*a*,5,6,7,8-hexahydro-3*H*-pyrido[1,2-*c*]pyrimidine (**139**) with anthranilic acids (71JMC878; 72USP3631046; 74USP3772230; 75USP3868372) or with ethyl 5-amino-3-methylisothiazole-4-carboxylate [76IJC(B)391] afforded the tetracyclic derivatives **140** and **141**, respectively.



The reaction of pyrido[1,2-*c*]pyrimidin-1-one (**142**) with 1 or 2 mol of maleic anhydride afforded the cycloadduct **143** and the polycyclic compound **144**, respectively (75IZV2608). The latter was formed from the cycloadduct **143**.



Reaction of 1-(nitromethylene)perhydropyrido[1,2-*c*]pyrimidine with *p*-chlorobenzenesulfonyl azide in dioxane at 80°C gave the tricyclic 1-nitro-6,6*a*,7,8,9,10-hexahydro-5*H*-pyrido[1,2-*c*][1,2,3]thiazolo[1,5-*a*]pyrimidine [79JCS(P1)2361].

IV. Synthesis

A. PYRIDO[1,2-*c*][1,3]OXAZINES AND THEIR BENZO DERIVATIVES

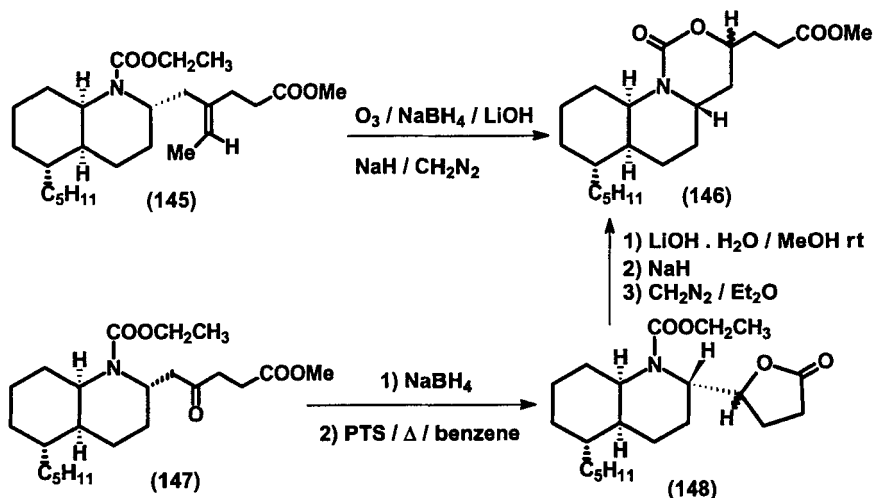
1. By Formation of One Bond α to the Bridgehead Nitrogen Atom [6+0(α)]

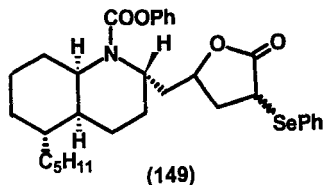
Treatment of 2-(2-vinyloxyethyl)pyridine with Br_2 in CCl_4 at 0°C gave 1-bromomethyl-2,3-dihydro-1*H*-pyrido[1,2-*c*][1,3]oxazinium bromide (86KGS1396).

2. By Formation of One Bond β to the Bridgehead Nitrogen Atom [6+0(β)]

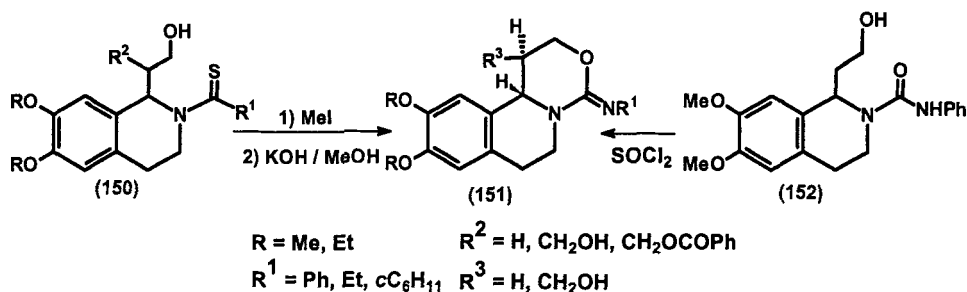
Perhydro[1,3]oxazino[3,4-*a*]quinolin-1-one (**146**) was prepared from perhydroquinoline (**145**) by sequential treatment with O_3 , NaBH_4 , LiOH , NaH , and finally diazomethane (80JA1454). Treatment of perhydroquinoline (**147**) with NaBH_4 , and then with *p*-toluenesulfonic acid in benzene under reflux, gave a 1 : 6 mixture of α - and β -lactones **148**. The β isomer of **148** was also converted to **146** in 93% yield with LiOH , NaH , and diazomethane (86CPB2380). Propionate **98** was obtained from **149** by reaction with LiOH and diazomethane [84JCS(CC)597; 86CPB2380].

4-Iminohexahydro[1,3]oxazino[4,3-*a*]isoquinolines (**151**) were obtained from tetrahydroisoquinolines (**150**) in good yields [83H(20)1325;





85GEP3510526; 90CB803; 93MI2, 93MIP1], or from **152** [83H(20)1325; 85GEP3510526; 92T4937; 93MIP1].



2-Ethoxycarbonyl-1-(2-hydroxyethyl)tetrahydroisoquinolines were cyclized to 1,2,4,6,7,11*b*-hexahydro[1,3]oxazino[4,3-*a*]isoquinolin-4-ones with phosgene in the presence of triethylamine (90T4039), or by mixing with NaOMe at 130°C (90T4039; 92T4937), or by treatment with NaIO₄-periodate in aqueous methanol in the presence of NaOH at 5°C (86CJC2205). When 2-(2-ethoxycarbonyl-1,2,3,4-tetrahydroisoquinol-1-yl)-1,3-propanediol was treated with boiling SOCl₂, a mixture of 1-chloromethyl- and 1-hydroxymethyl-1,2,4,6,7,11*b*-hexahydro[1,3]oxazino[4,3-*a*]isoquinolin-4-ones was obtained (90T4039; 93MI2).

Cyclization of 2-(1-alkoxycarbonyl-2-piperidinyl)ethanols with mesyl chloride in pyridine (91T3805) or in the presence of NEt₃ [88CPB1597; 90H(30)855], with NaH [83H(20)601; 85H(23)831] or with KOH in boiling methanol (91CJC211), led to perhydropyrido[1,2-*c*][1,3]oxazin-1-ones.

3. By Formation of One Bond γ to the Bridgehead Nitrogen Atom [6+0(γ)]

Cyclization of 3-(2-oxo-3,1-benzoxazin-1-yl)propionic acid in PPA at 100–120°C gave 6,7-dihydro-1*H*,3*H*-5*H*-pyrido[3,1-*ij*][3,1]benzoxazine-3,7-dione (87EUP239129; 90CPB1575). Asymmetric bromolactonization of 2-(2,3-dimethylacryloyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid in DMF in the presence of NBS afforded a diastereomeric mix-

tures of 3-methyl-3-(2-bromoethyl)-1,3,4,6-tetrahydro-7*H*-[1,4]oxazino[1,3-*b*]isoquinoline-1,4-diones (77CL1109).

4. By Formation of Two Bonds from [5+1] Atom Fragments

Goodson-Christopher cyclization of 2-(2-piperidyl)ethanols with aldehydes yielded perhydropyrido[1,2-*c*][1,3]oxazines [17CB1407; 50JA358; 54JA2431; 56BRP756686, 56CLY1180; 57CLY927; 58CLY2081, 58N516; 60AP74, 60BRP856357, 60CCC2179, 60JOC2028, 60M840; 62USP3031454; 63AP38; 65RTC1367; 66MI2; 67RZC1389, 67TL2471; 68CJC1105, 68T4423; 70LA(737)24, 70T1217, 70T3941; 71T2055; 72JCS(CC)1152; 76IJC(B)777, 76JCS(P2)418, 76OMR(8)258; 78TL4647; 80BRP2071653; 85T2891; 87T935; 88TL1691; 89TL1947; 95TA2149]. When ketones or cyclic ketones were applied, disubstituted and spiro derivatives were obtained [66AP997, 76IJC(B)777; 85GEP3439131; 90EUP373531].

Reaction of racemic and meso-1,3-di(2-piperidyl)-2-propanone with 40% formaldehyde at pH 5 gave dodecahydro-3,3'-bi-1*H*,3*H*-pyrido[1,2-*c*][1,3]oxazines [71LA(753)27].

Similarly, starting from the appropriate 2-substituted ethanols, partly or fully saturated [1,3]oxazino[3,4-*b*]isoquinolines [77JCS(P2)370; 80HCA1158], [1,3]oxazino[4,3-*a*]isoquinolines [66AP997; 76OMR(8)258; 77JCS(P2)370; 85GEP3439131; 90CB803; 92T4937; 94JAP(K)94/41142], and [1,3]oxazino[3,4-*a*]quinolines [77JCS(P2)1592; 93JCR(S)170] were prepared with aldehydes [66AP997; 76BCJ837, 76OMR(8)258; 79JHC21; 92T4937] or with a form of formaldehyde. Pyrido[1,2-*c*][1,3]benzoxazines [70T1217; 76BCJ837, 76IJC(B)975; 77USP4025512; 79JHC21; 91KGS124] and pyrido[3,2,1-*ij*]benzoxazines [80JCS(P2)1778; 84OMR(22)424; 90EUP373531] were prepared from 2-(2-piperidyl)cyclohexenol, 2-(hexahydro- or tetrahydro-2-pyridyl)phenols, and 8-hydroxymethylperhydroquinolines on treatment with aldehydes (76BCJ837; 79JHC21; 90EUP373531) or with a form of formaldehyde.

Instead of formaldehyde, *N,N,N',N'*-tetramethylmethylenediamine (80HCA1158) or dibromomethane [76IJC(B)975] could also be applied.

Perhydropyrido[1,2-*c*][1,3]oxazin-1-ones were prepared in the reaction of the appropriate 2-(2-piperidyl)ethanols and ethyl chloroformate (63AP38) in the presence of sodium ethylate in boiling benzene, or when 2-(2-piperidyl)ethanol was reacted with dimethyl carbonate in the presence of sodium methylate (91T1311). 1-Hydroxymethyl-9,10-dimethoxy-1,2,4,6,7,11*b*-hexahydro-[1,3]oxazino[4,3-*a*]isoquinoline-4-one and 4-thione were prepared from 1-[bis(hydroxymethyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with ethyl chloroformate in the presence of sodium methylate, and thiophosgene in the presence of NEt_3 , respectively

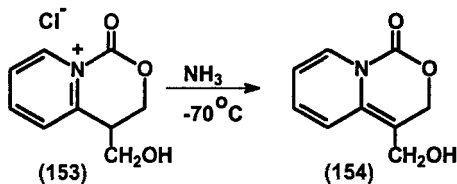
(85GEP3510526). Reaction of 2-(2-hydroxy-2-substituted ethyl)-1,2,3,4-tetrahydroquinolines with diethyl carbonate at 100°C in toluene in the presence of sodium methylate gave mixtures of epimers of 3-substituted 1,3,4,4a,5,6-hexahydro[1,3]oxazino[3,4-*a*]quinolin-1-ones (89EUP322263).

Optically active and racemic 1-ethylideneperhydro[1,3]oxazino[3,4-*b*]isoquinolines (**42**) were prepared in good yields from the appropriate 3-(2-hydroxyethyl)perhydroisoquinoline with *N,N*-dimethylpropionamide dimethyl acetal (80HCA1158).

Optically active *cis*-3,4a-H-1,3,4,4a,5,6-hexahydropyrido[1,2-*c*][1,3]oxazine-1,6-diones were obtained from (+)-2-(2-hydroxy-2-phenylethyl)- and (+)-2-(2-hydroxypentyl)-1,2,3,4-tetrahydropyridin-4-one with 1,1'-carbonyldiimidazole in THF in the presence of triethylamine (93JA8851, 93JOC5035).

The 1-imine derivatives of 4-phenylperhydropyrido[1,2-*c*][1,3]oxazines were prepared from *erythro*- and *threo*-2-(2-piperidyl)-2-phenylethanols with cyanogen bromide followed by treatment with hydrogen chloride in boiling ethanol (73AP284).

Treatment of 8-hydroxymethyl-1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroquinoline-8-carboxylic acid, or 1-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinolines with COCl₂ in the presence of a base furnished 1,5,6,7-tetrahydro-3*H*-pyrido[3,2,1-*ij*][3,1]benzoxazin-3-one (92JMC1076), the -1,3-dione (**102**) (78JHC645), and 1,2,4,6,7,11*b*-hexahydro[1,3]oxazino[4,3-*a*]isoquinolin-4-ones (92T4937), respectively.



1-Oxopyrido[1,2-*c*][1,3]oxazin-3-one (**153**) was prepared from 2-(2-pyridyl)-1,3-propanediol by reaction with COCl₂ in the presence of NEt₃ at -30°C (92JOC5764). When 6 mol COCl₂ was used and the reaction mixture was treated with gaseous NH₃ at -70°C, **154** was obtained in excellent yield.

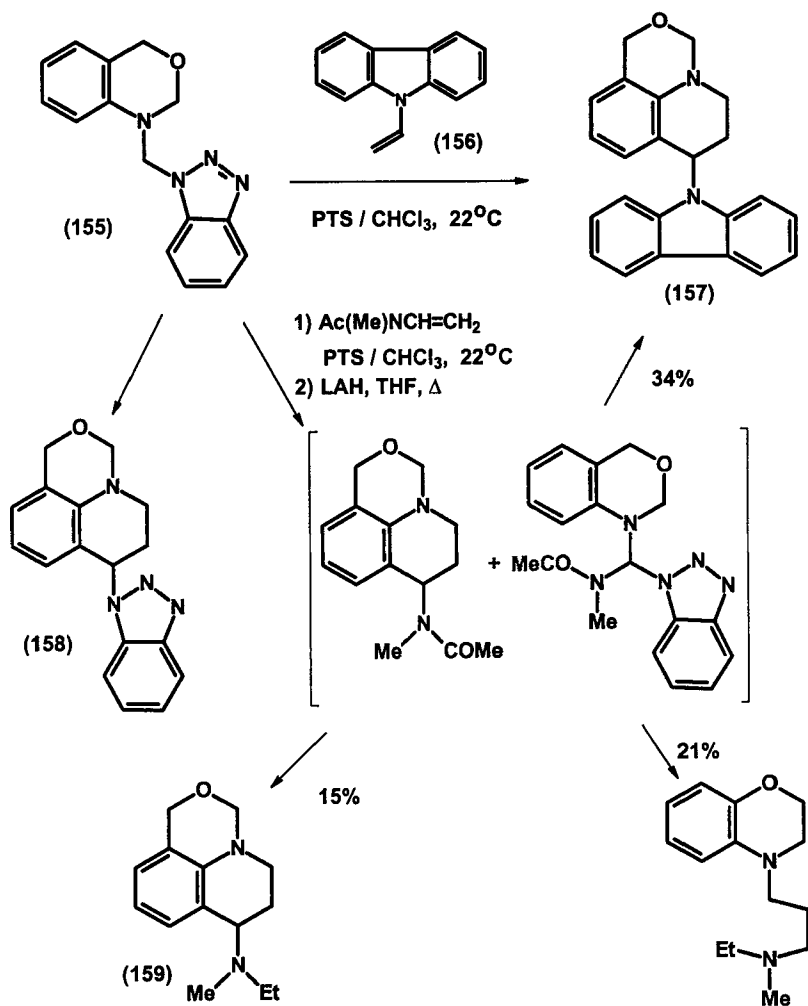
5. By Formation of Two Bonds from [4+2] Atom Fragments

7-Substituted 6,7-dihydro-1*H*,3*H*,5*H*-pyrido[3,2,1-*ij*][3,1]benzoxazines (**157–159**) were prepared from 1-(1-benzotriazolyl)-1,2-dihydro-3*H*-

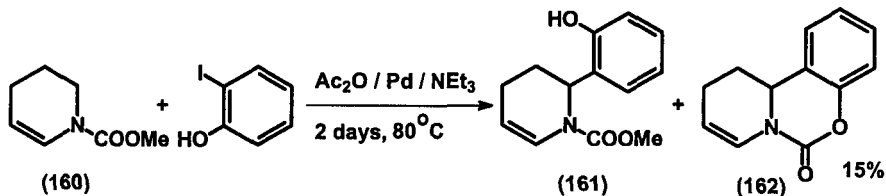
[3,1]benzoxazine (**155**) with 9-vinylcarbazole (**156**) and *N*-methyl-*N*-vinylacetamide (Scheme 15) (95JOC3993).

6. By Formation of Two Bonds from [3+3] Atom Fragments

The palladium-catalyzed arylation of cyclic enamide **160** with 2-iodophenol furnished a ca. 2:1 mixture of **161** and pyrido[1,2-*c*][1,3]benzoxazin-6-one (**162**) (90JOC2464).



SCHEME 15

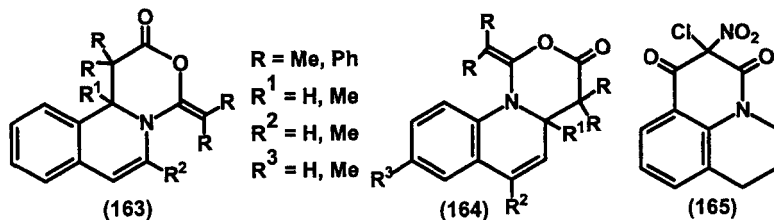


7. By Formation of Three Bonds from [3+2+1] Atom Fragments

The reaction of 1-cyanomethylene-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline with 35% aqueous formaldehyde in the presence of 2 *N* NaOH at 65°C afforded [1,3]oxazino[4,3-*a*]isoquinoline (**100**) (73JHC435).

8. By Formation of Three Bonds from [2+2+2] Atom Fragments

[1,3]Oxazino[4,3-*a*]isoquinolin-2-ones (**163**) [10LA(374)1; 67JCS(C)1569; 68AGE826; 71JOC2211; 75JCS(P1)1001] and [1,3]oxazino[3,4-*a*]quinolin-3-ones (**164**) [06CB968; 65JCS(CC)574; 66JCS(CC)262; 67JCS(C)1569; 71JOC2211; 75JCS(P1)1001] were prepared in exothermic cycloaddition reactions of isoquinolines and quinolines, respectively, with dimethylketene [67JCS(C)1569; 71JOC2211] and diphenylketene [68AGE826; 75JCS(P1)1001]. The 6,7-dihydro derivative of **65** was obtained in 17% yield, accompanied by other products, in the reaction of 3,4-dihydroisoquinoline *N*-oxide and dimethylketene in ethyl acetate [87JCS(P1)1635].



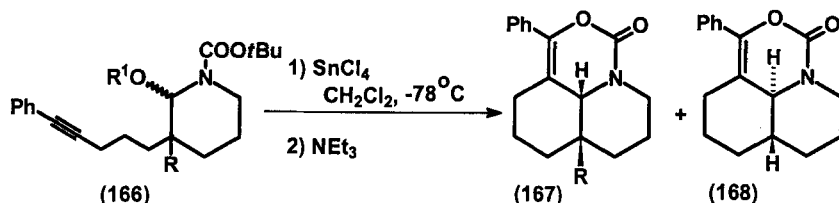
9. Ring Transformations

Treatment of chloronitro derivative **165** with 2 *N* NaOH at 75–80°C gave pyrido[3,2,1-*ij*][3,1]benzoxazine-1,3-dione (**102**) (64M59).

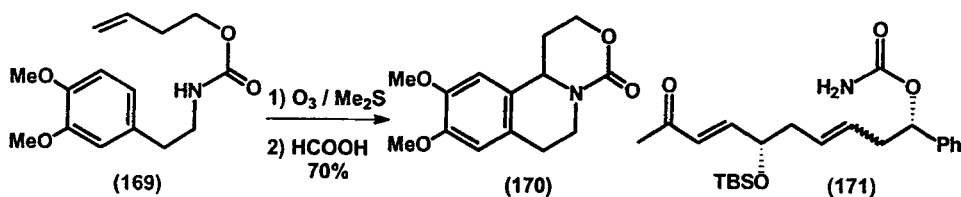
Ring expansion of 2,2-diphenyl-8-methylperhydroisoxazolo[2,3-*a*]pyridinium salt on the action of NaOH furnished 3,3-diphenylperhydro-pyrido[1,2-*c*][1,3]oxazine in good yield (91G393).

10. Miscellaneous

The Lewis acid-promoted intramolecular cyclocondensation of piperidine epimers (**166**, R = H) led to the formation of a 2 : 1 mixture of epimers **167** (R = H) and **168** with a preference for *cis*-fused tricycles (**167**, R = H) (90JOC1447). The 3-methylpiperidine derivative (**166**, R = Me) gave only the *cis*-fused epimer (**167**, R = Me).



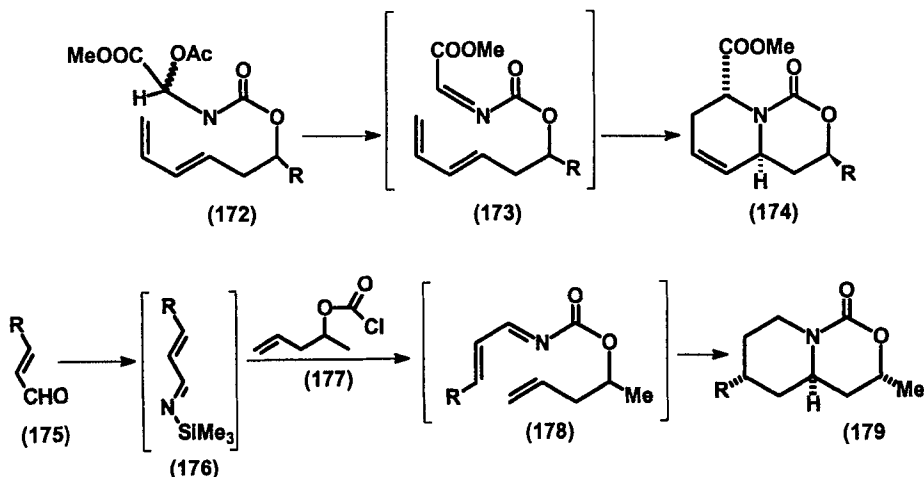
Ozonolysis of carbamate **169** and successive workup with dimethyl sulfide, followed by cyclization with formic acid, yielded hexahydro-3*H*-[1,3]oxazino[4,3-*a*]isoquinolin-4-one (**170**) (85SC883).



The intramolecular conjugate addition of either a 1 : 2 mixture of *E* and *Z* isomers or pure *Z* isomer of **171** proceeded smoothly with potassium *tert*-butoxide (0.3 equiv) in THF at low temperature (between -20 and -58°C) and gave an 8 : 11 mixture of pyrido[1,2-*c*][1,3]oxazines (**33** and **34**) in 87% yield (96SL100).

Intramolecular hetero-Diels-Alder cycloaddition of *N*-acylimines **173** and **178**, prepared *in situ* from an isomeric mixture of methylol acetates (**172**) by heating (81JA7573; 84JA3240) or from chloroformate (**177**) and *N*-trimethylsilylimines (**176**) derived from aldehydes **175** (91TL4371), respectively, diastereoselectively afforded only one type of the cycloaddition products **174** and **179**, containing *trans*-fused bicycles.

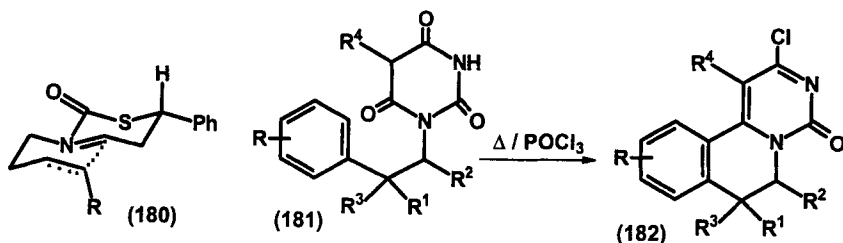
Treatment of dodecahydro-3,3'-bi-1*H*,3*H*-pyrido[1,2-*c*][1,3]oxazines with 2% sodium amalgam in aqueous acetic acid gave 3-[(2-piperidyl)methyl]perhydropyrido[1,2-*c*][1,3]oxazines [71LA(753)27].



B. PYRIDO[1,2-*c*][1,3]THIAZINES AND THEIR BENZO DERIVATIVES

1. By Formation of One Bond β to the Bridgehead Nitrogen Atom [6+0(β)]

Cyclization of 3-(3-butenyl)-4-ethoxy-6,6-dimethyl- and 3-(3-alkenyl)-4-ethoxy-6-phenyltetrahydro-1,3-thiazin-2-ones in formic acid at room temperature afforded 3,3-dimethylperhydropyrido[1,2-*c*][1,3]thiazine-1,6-dione and *cis*-3,4*a*,5,6-*H*-5-alkyl-7-formyloxy-3-phenylperhydropyrido[1,2-*c*][1,3]thiazin-1-ones (85T2007). In the latter cases, the reaction proceed via a “double chair” transition state (180) containing a phenyl ring in an equatorial position.



2. By Formation of One Bond γ to the Bridgehead Nitrogen Atom [6+0(γ)]

Heating three *N*-substituted 3-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline-2-thioamides in boiling 6 *N* hydrochloric acid gave 1-(substituted

imino)-1,3,4,4*a*,5,10-hexahydro[1,3]thiazino[3,4-*b*]isoquinolines (79GEP 2848926; 80GEP3017865; 85MIP1). Similarly, 1-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline-2-thioamides in boiling ethanol containing hydrogen chloride afforded 4-(substituted imino)-1,2,4,6,7,11*b*-hexahydro[1,3]-thiazino[4,3-*a*]isoquinolines [83H(20)1325], whereas 1-[bis(hydroxymethyl)-methyl]tetrahydroisoquinolines and the mono-*O*-benzoyl derivative yielded 1-hydroxymethyl- and 1-(benzoyloxy)methyl-4-(substituted imino)-1,2,4,6,7,11*b*-hexahydro[1,3]thiazino[4,3-*a*]isoquinolines (85GEP3510526; 90CB803; 93MI2).

Mixtures of 1-(3-chloropropyl)-1,4-dihydro-2*H*-[3,1]benzothiazin-2-ones or their 3,3-dioxides and anhydrous AlCl₃ were stirred at ambient temperature for 30 min, and then at 170–180°C for 1 h, to give 1,5,6,7-tetrahydro-3*H*-pyrido[3,2,1-*ij*][3,1]benzothiazin-3-ones and their 2,2-dioxides [88JAP(K)88/170385].

3. By Formation of Two Bonds from [5+1] Atom Fragments

1-Iminoperhydropyrido[1,2-*c*][1,3]thiazine hydrobromides were prepared when 2-(2-hydroxyethyl)piperidines were treated with gaseous HBr followed by PBr₃ in carbon tetrachloride, and the 2-(2-bromoethyl)piperidines were reacted with thiourea in boiling ethanol [70T3941; 82OMR(20)239].

The reactions of 2-(2-mercaptoethyl)piperidines and aldehydes afforded perhydropyrido[1,2-*c*][1,3]thiazines [70T3941; 82OMR(20)239]. In an exothermic reaction, 1-(2-mercaptoethyl)-1,2,3,4-tetrahydroisoquinoline and 40% aqueous formaldehyde yielded 1,2,4,6,7,11*b*-hexahydro[1,3]thiazino[4,3-*a*]isoquinoline [77JCS(P2)370]. The similar reaction with 4-nitrobenzaldehyde in boiling benzene furnished the *cis*-4,11*b*-*H*-1-(4-nitrophenyl) derivative [76OMR(8)258].

4. By Formation of Two Bonds from [4+2] Atom Fragments

1-(Substituted imino)perhydropyrido[1,2-*c*][1,3]thiazines were obtained when 2-(2-hydroxyethyl)piperidine was reacted with aryl and aralkyl isocyanates and then the thioureas were cyclized by heating in aqueous 48% hydrogen bromide [76IJC(B)770]. 1,3,4,4*a*,5,10-Hexahydro[1,3]thiazino[3,4-*b*]isoquinoline-1-thione was prepared when 3-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline was reacted with CS₂ in pyridine in the presence of NEt₃, and the reaction mixture was then treated with mesyl chloride (79GEP2848926). Perhydropyrido[1,2-*c*][1,3]thiazine-1-thione was prepared in 91% yield in the reaction of 2-(2-chloroethyl)piperidine hydrochloride and CS₂ in DMF in the presence of K₂CO₃ at room temperature (63JOC981). When 2-(2-chloro- or 2-bromoethyl)piperidine hydrohalides

were reacted with sodium dimethyldithiocarbamate, only the substitution of the halo atom occurred (63JOC981). 3,5,6,7-Tetrahydro-1*H*-pyrido[3,2,1-*ij*][3,1]benzothiazine-3-thiones and -3-ones were prepared from 8-hydroxymethyl-1,2,3,4-tetrahydroisoquinolines by treatment with CS₂ or COS in boiling ethanol in the presence of NaOH (87EUP239927).

5. By Formation of Three Bonds from [2+2+2] Atom Fragments

Tetramethyl 2,3-dimethoxy-6,11*a*-dihydropyrido[1,2-*c*][1,3]benzothiazine-8,9,10,11-tetracarboxylate was prepared in the reaction of 6,7-dimethoxy-2*H*-1,3-benzoxazine and dimethyl acetylenedicarboxylate in diethyl ether at 0°C [82H(19)489].

6. Ring Transformations

The reaction of 1-(substituted imino)-9,10-dimethoxy-1,2,4,6,7,11*b*-hexahydro[1,3]oxazino[4,3-*a*]isoquinoline with P₄S₁₀ at 150–170°C gave 1-(substituted imino)-9,10-dimethoxy-1,2,4,6,7,11*b*-hexahydro[1,3]thiazino[4,3-*a*]isoquinoline [83H(20)1325; 85GEP3510526; 90CB803].

3,5,6,7-Tetrahydro-1*H*-pyrido[3,2,1-*ij*][3,1]benzothiazine-1,3-dithione was prepared from 3,5,6,7-tetrahydro-1*H*-pyrido[3,2,1-*ij*][3,1]benzoxazine-1,3-dione with P₄S₁₀ in boiling pseudocumene (78JHC645).

C. PYRIDO[1,2-*c*]PYRIMIDINES AND THEIR BENZO DERIVATIVES

1. By Formation of One Bond α to the Bridgehead Nitrogen Atom [6+0(α)]

Hydrogenation of ethyl *N*-[2-(2-pyridyl)ethyl]carbamate in ethanol over Raney Ni at 130°C and 120 atm gave perhydropyrido[1,2-*c*]pyrimidin-1-one (67YZ663). Cyclization of ethyl *N*-[2-(1,2,3,4-tetrahydro-2-quinolyl)ethyl]carbamate at 190–200°C afforded 2,3,4,4*a*,5,6-hexahydro-1*H*-pyrimido[1,6-*a*]quinolin-1-one (60YZ1414), whereas that of 1-(2-benzamidoethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline in boiling toluene with phosphoryl chloride led to 4-phenyl-9,10-dimethoxy-6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinoline (63YZ1043).

Hydrogenation of 1-acylamidinomethylene-1,2,3,4-tetrahydroisoquinoline (**48**, R = Me, R¹ = Ph) over Pd/C gave 2-amino-4-phenyl-9,10-dimethoxy-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinoline via **49** (R = Me, R¹ = Ph) (90CB493). When an ethanolic solution of 1-[(benzoylamidino)methylene]tetrahydroisoquinoline (**48**, R = Me, R¹ = Ph) was evaporated

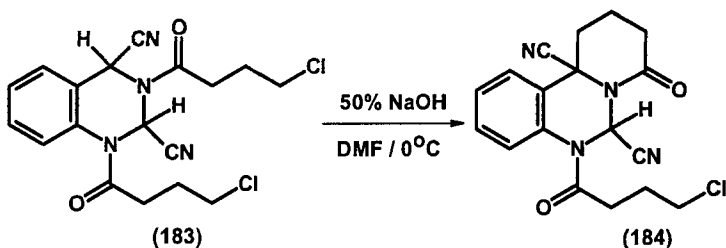
at atmospheric pressure and the residue was heated for another 0.5 h, **51** hydrate ($R = \text{Me}$, $R^1 = \text{Ph}$) was obtained (90CB493). When **48** was heated in boiling 2% hydrochloric acid, hydrochloride salts of monohydrates of **51** were obtained (86MIP1).

2. By Formation of One Bond β to the Bridgehead Nitrogen Atom [$6+0(\beta)$]

2-Chloro-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-ones (**182**) were obtained by the cyclization of barbituric acid derivatives **181** [80GEP2847693; 84EUP124893, 84JMC1470; 86HCA1671; 89H(29)1929]. Cyclization in PPA afforded 2,4-dioxo-2,3,6,7-tetrahydro-4*H* derivatives (80GEP2847693). 1-Substituted 4-phenyl-4-[2-(*N,N*-di(2-propylamino)-4,4*a*,5,6,7,8-hexahydro-3*H*-pyrido[1,2-*c*]pyrimidin-3-ones were prepared by the cyclization of α -(1-acyl-2-piperidyl)- α -phenyl- α -[2-(*N,N*-di(2-propylamino)ethyl]acetamides with powdered potassium hydroxide in boiling acetone or DMSO (87EUP215477).

Cyclization of 1-[*N*-(un)substituted amino(thio)carbonyl]-2-[phenyl (methoxycarbonyl)methyl]piperidines in boiling ethanol containing hydrogen chloride gave 4-phenyl-2-(un)substituted perhydropyrido[1,2-*c*]pyrimidine-1,3-diones (64JMC146).

Cyclization of Reissert compound **183** furnished pyrimido[1,2-*c*]quinazolin-4-one (**184**) (89JHC1357).



Cyclization of 2-aryl-2-(2-piperidinyl)acetamide (**185**) in the presence of KOH afforded 1-substituted 4,4*a*,5,6,7,8-hexahydro-3*H*-pyrido[1,2-*c*]pyrimidin-3-ones (**108**) (85JMC1285).

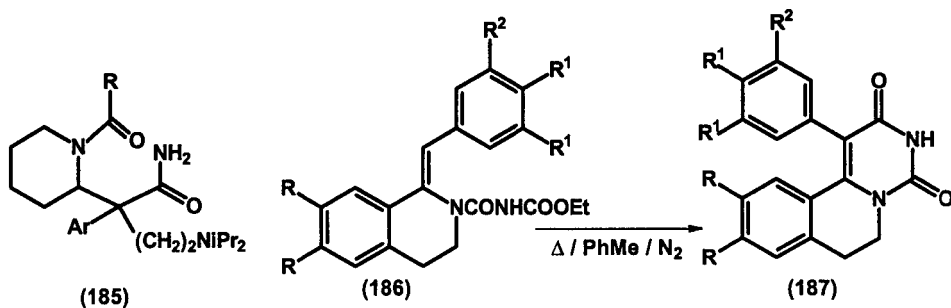
3. By Formation of One Bond γ to the Bridgehead Nitrogen Atom [$6+0(\gamma)$]

Cyclization of alkyl 2-[1-amino(thio)carbonyl]-2-piperidyl]acetates under acidic or basic conditions gave 1,3-dioxo- and 1-thioxo-3-

oxoperhydropyrido[1,2-*c*]pyrimidines (56CB1642; 64JMC146). 2,4-Dioxo- and 2-oxo-4-thioxo-1,3,4,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines [69IJC684, 69YZ649; 71JAP71/09467; 75MI1; 76IJC(B)784] were prepared similarly. 2-Substituted 4-phenyl-1,3-dioxo- and 1-thioxo-3-oxoperhydropyrido[1,2-*c*]pyrimidines could be prepared similarly in one-pot reactions, when aryl iso(thio)cyanates were reacted with methyl 2-phenyl-2-(2-piperidinyl)acetate, and the reaction products were subsequently cyclized without isolation (64JMC146). Cyclization of α -(1-amino-carbonyl-2-piperidyl)- α -phenyl- α -[2-(*N,N*-di(2-propyl)amino)ethyl]acetonitrile and its *N*-[2-(3,4-dimethoxyphenyl)ethyl]-substituted derivatives in the presence of sodium hydride in boiling tetrahydrofuran gave 3-amino-4,4*a*,5,6,7,8-hexahydro-1*H*- and 2-substituted 3-iminoperhydropyrido[1,2-*c*]pyrimidin-1-ones, respectively (87USP4680295).

Cyclization of 6,7-diethoxy-2-propylaminocarbonyl-1,2,3,4-tetrahydroisoquinoline-1-acetonitrile by NaOMe in boiling methanol afforded 9,10-dimethoxy-2-imino-3-propyl-1,2,4,6,7,11*b*-hexahydro-pyrimido[6,1-*a*]isoquinolin-4-one (95S863).

1-Aryl-3,4,5,6-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-2,4-diones (**187**) were obtained from 1-arylidene-2-ethoxycarbonylamino-carbonyltetrahydroisoquinolines (**186**) (84T4003).



Heating 3-[(3-benzyl-6-(un)substituted-1,2,3,4-tetrahydroquinazolin-1-yl)]propionic acids in PPA at 100°C resulted in 2-benzyl-1,2,3,5,6,7-hexahydropyrido[3,2,1-*ij*]quinazolin-7-one. When the cyclization was carried out in the presence of acetic acid, the 9-acetyl derivative was produced (72MI1).

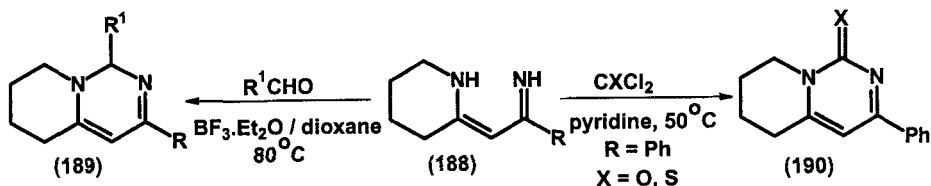
Treatment of 1-cyanomethyl-2-[(propylamino)carbonyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with sodium methoxide in boiling methanol afforded 2-imino-3-propyl-9,10-dimethoxy-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-one (95S863).

4. By Formation of Two Bonds from [5+1] Atom Fragments

Perhydropyrido[1,2-*c*]pyrimidines and their -1-ones and -1-thiones were prepared from the appropriate 2-(2-piperidyl)ethylamines or their *N*-substituted derivatives by treatment with aldehydes [59CB637; 62JOC1970; 67YZ663; 69JHC181; 70T701; 71JAP71/16753; 73OMR(5)397; 90TL4543], Et₂CO₃ (62JOC1970), or CS₂ (62JOC1970; 71JMC878; 72USP3631046; 74USP3772230; 75USP3868372), respectively. When cyclohexanone was used, a 1,1-spiro derivative of perhydropyrido[1,2-*c*]pyrimidine was obtained (67YZ663). Similarly, 2-methyl-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrimido[1,6-*a*]quinoline [79JCS(P2)581], 1,3,4,5,6,7,11*b*-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines (59YZ1008; 78FES237; 90KGS1665; 95MI4), and their -4-ones (77SAP77/06706; 78GEP2720085; 81FRP2470130; 84JMC1470, 84USP4482556; 95MI4) were prepared from the appropriate 2-(1,2,3,4-tetrahydroquinolin-2-yl)- and 2-(1,2,3,4-tetrahydroisoquinolin-1-yl)ethylamines. 1-Substituted 4,4*a*,5,6,7,8-hexahydro-3*H*-pyrido[1,2-*c*]pyrimidines were obtained from the reactions of 2-(2-piperidyl)ethylamine and imino ester hydrochlorides in boiling ethanol (67YZ663). 2-(1,2,3,4-Tetrahydroisoquinolin-1-yl)ethylamine and triethyl orthoacetate reacted in boiling butanol to afford 4-methyl-1,6,7,11*b*-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline (90KGS1665).

4-Phenyl-4-{{*N,N*-di(2-propyl)amino}ethyl}perhydropyrido[1,2-*c*]pyrimidine-1,3-dione was obtained in the reaction of α -phenyl- α -{{*N,N*-di(2-propyl)amino}ethyl}-2-piperidineacetamide and 1,1'-carbonyldiimidazole in the presence of sodium hydride (87USP4680295). 6-Dialkylamino-1,2,3,5,6,7-hexahydropyrido[3,2,1-*ij*]quinazolin-3-ones were prepared via the reaction of 8-aminomethyl-3-(alkylamino)-1,2,3,4-tetrahydroquinoline and 1,1'-carbonyldiimidazole in THF (90MIP2; 92JMC1076).

The reactions of 2-piperidineacetamides with aqueous formaldehyde [68BRP1114397; 72JCS(P2)1920] or with *N,N*-dimethylcarboxamide dialkyl acetals (84EUP104647; 85JMC1285) gave perhydro- or 4,4*a*,5,6,7,8-hexahydro-3*H*-pyrido[1,2-*c*]pyrimidin-3-ones, respectively. Reaction of 1-chlorocarbonyl-2-[1-cyano-1-phenyl-3-{{*N,N*-di(2-propyl)amino}propyl}]piperidine with ammonium hydroxide or primary amines at 80°C afforded 4-phenyl-4-{{2,*N,N*-di(2-propyl)amino}ethyl}-3-amino-4,4*a*,5,6,7,8-hexahydro-1*H*- and 3-iminoperhydropyrido[1,2-*c*]pyrimidin-1-ones, respectively (87USP4680295). 1,3-Dioxo- and 3-oxo-1-thioxo-2,3-dihydro-1*H*-pyrido[1,2-*c*]pyrimidines were obtained in the reactions of 2-(2-pyridyl)acetamides with Et₂CO₃ and CSCl₂, respectively (57HCA1319). 1,3,4,6,7,11*b*-Hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-2-ones were produced when *N*-substituted 2-(1,2,3,4-tetrahydroisoquinolin-1-yl)acetamides were treated with aldehydes [61JMC505; 62USP3021331; 77JCS(P2)370; 90JHC957].



5,6,7,8-Tetrahydro-1*H*-pyrido[1,2-*c*]pyrimidines **189** and -1-one **190** were prepared from cyclic aminoazadienes **188** by reaction with aldehydes and triphosgene, respectively (92SL563). 4-Cyano-5,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*]pyrimidin-3-one and its 1-methyl and 5-dimethylaminomethylene derivatives were prepared in the reactions of 2-[cyano(aminocarbonyl)-methylene]piperidine with triethyl orthoformate in acetic anhydride with *N,N*-dimethylacetamide diethyl acetal, or with *N,N*-dimethylformamide diethyl acetal (80KGS416, 80KGS1120; 82KGS518).

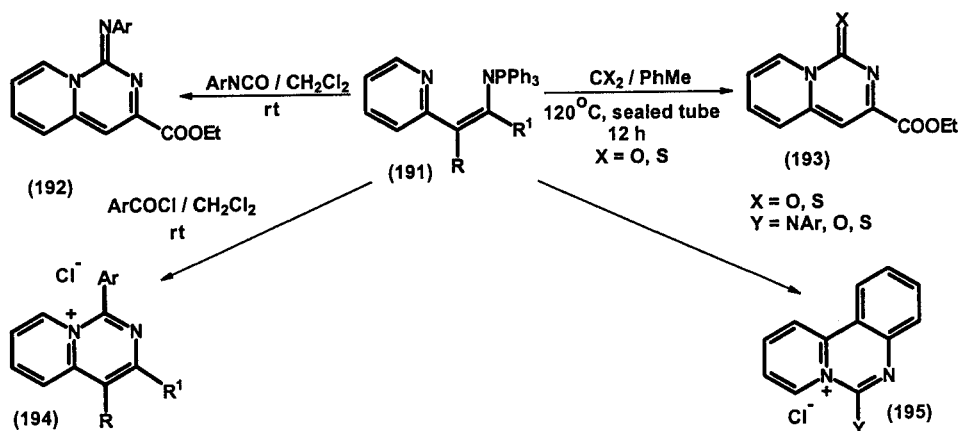
The reactions of 1-aminocarbonylmethylene-3,4-dihydro- and 1,2,3,4-tetrahydroisoquinolines with *N,N*-dimethylcarboxamide diethyl acetals, triethyl orthoformate, and diethyl carbonate yielded 6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinolin-2-ones [81KFZ(5)44; 82KGS1095; 84JMC1470] and 9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-2,4-dione (84JMC1470), respectively. A mixture of 1-ethoxycarbonyl-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-2,4-dione and 1-[cyano(ethoxycarbonyl)methylene]-1,2,3,4-tetrahydroisoquinoline was obtained when 6,7-dimethoxy-1-aminocarbonylmethylene-1,2,3,4-tetrahydroisoquinoline was reacted with ethyl chloroformate in methylene chloride in the presence of pyridine (84JMC1470).

1-Aryl-9-methoxy-1,2,3,5,6,7-hexahydropyrido[3,2,1-*ij*]quinazolin-3-ones were prepared from 1-aminocarbonyl-6-methoxy-1,2,3,4-tetrahydroquinoline on treatment with aromatic aldehydes in boiling benzene in the presence of methanesulfonic acid (73USP3709887).

3-Methyl-5-methoxy-2-phenyl-2,4*a*,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidine-1-thione was obtained in the reaction of 2-acetonil-3-methoxypiperidine and phenyl isothiocyanate in boiling methylene chloride (55JOC136).

Reductive alkylation of 3-(2-nitro-1-hydroxyethyl)isoquinoline over Pd/C in the presence of hydrogen and acetone afforded a mixture of 1,1-dimethyl-4-hydroxy-2,3,4,4*a*,5,10-hexahydro-1*H*-pyrimido[1,6-*b*]-*b*]isoquinoline and 3-[1-hydroxy-3-(*N*-isopropylamino)propyl]-1,2,3,4-tetrahydroisoquinoline (72JMC49).

Heating 2-(2-pyridyl)benzodiazonium tetrafluoroborate in a nitrile at $80^\circ C$ gave 6-substituted pyrido[1,2-*c*]quinazolinium tetrafluoroborates (72GEP2043665).



The reactions of iminophosphorane (**191**, $\text{R} = \text{H}$, $\text{R}^1 = \text{COOEt}$) with aryl isocyanate, CO_2 , CS_2 , and aroyl chloride gave pyrido[1,2-*c*]pyrimidines **192**, **193**, and **194** ($\text{R} = \text{H}$, $\text{R}^1 = \text{COOEt}$), respectively (92T4601). The similar reactions of iminophosphorane **191** [$\text{R} = \text{R}^1 - (\text{CH}=\text{CH})_2$] afforded tricyclic pyrido[1,2-*c*]quinazolinium derivatives **194**, [$\text{R} = \text{R}^1 = -(\text{CH}=\text{CH})_2$] and **195**.

5. By Formation of Two Bonds from [4+2] Atom Fragments

Perhydropyrido[1,2-*c*]pyrimidine-1,3-diones were prepared in the reaction of alkyl 2-piperidineacetate with ethyl urethane in diethyl ether in the presence of sodium (56CB1642), by heating with KOCN in hydrochloric acid (59CB637; 64JMC146). 1-Thioxoperhydropyrido[1,2-*c*]pyrimidin-3-one was obtained when ethyl 2-piperidine acetate was reacted with KSCN in acidified ethanol (59CB637). Reaction of methyl 2-piperidyl acetate with aryl isocyanates yielded 2-arylperhydropyrido[1,2-*c*]pyrimidine-1,3-diones (94GEP4225629). 2-Phenyl-1-thioxo- and 2,4-diphenyl-1-thioxoperhydropyrido[1,2-*c*]pyrimidin-3-ones were prepared in the reactions of 2-piperidineacetic acid (75CJC41) and its 2-phenyl-substituted methyl ester derivative (64JMC146) with alkyl or aryl iso(thio)cyanates. Reaction of ethyl cyclohexylideneacetate and cyclohexylidenemalononitrile with iso(thio)cyanates afforded 2-substituted 2,3,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidine-1,3-diones [87CR(305)441] and 2-substituted 4-cyano-3-imino-2,3,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidin-1-ones (78MI1; 90MI3), respectively. In the latter cases the 3-imino group was acylated when an excess of isocyanates was applied (78MI1). 2,4-Dioxo-

and 2-oxo-4-thioxo-1,3,4,6,7,11*b*-hexahydro-, 2-oxo-4-amino- and 2-oxo-4-substituted 1,6,7,11*b*-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolines were prepared in the reactions of 2-(6,7-dialkoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)acetates or -acetic acids with urea, KOCN, and (ω -chloroalkyl)isocyanates, with phenyl isothiocyanate, *S*-methylisothiourea, and imino ethers, respectively [59YZ1008; 69IJC684; 76IJC(B)784; 79IJC(B)277; 84JHC149; 95S863].

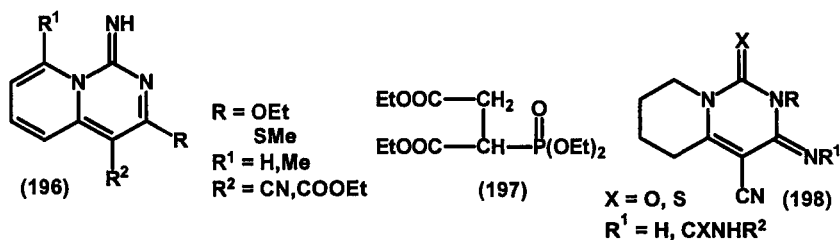
2-Acyl-2,3-dihydro-1*H*-pyrido[1,2-*c*]pyrimidin-4-ones were obtained when 2-vinylpyridine was reacted with acyl isocyanates (75IZV2608). Cyclocondensation of 3-methoxy-2-(2-oxopropyl)piperidine and phenyl isothiocyanate in boiling ethylene dichloride afforded 3-methyl-5-methoxy-2-phenyl-2,4*a*,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidine-1-thione (55JOC136).

The reaction of 2-phenyl-5(4*H*)-oxazolone and 4-[2-(*E*)-dimethylaminoethenyl]-6-methyl-2-methoxypyrimidine in boiling acetic acid afforded 7-benzamido-3-methyl-1-methoxy-8*H*-pyrido[1,2-*c*]pyrimidin-8-one (91BSB533).

The reaction of 1-(2-methyl-3-furyl)-6,7-dimethoxy-3,4-dihydroisoquinoline with phenyl isocyanate gave an *E*-*Z* mixture of 3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-one (**132**) (86CB2553).

6. By Formation of Two Bonds from [3+3] Atom Fragments

1-Imino-1*H*-pyrido[1,2-*c*]pyrimidines (**196**) were prepared via the reactions of 2-pyridineacetonitriles and 2-pyridineacetates with dimethyl cyanoamidedithiocarboxylate and *O*-ethyl and *O*-ethyl-*S*-methyl cyanoamidedithiocarboxylate (74CPB2765; 75YZ13; 78YZ623).



Horner-Witting reaction of the succinate (**197**) with 4-formylpyrimidine led to ethyl 8-oxo-8*H*-pyrido[1,2-*c*]pyrimidine-6-carboxylate (80LA542).

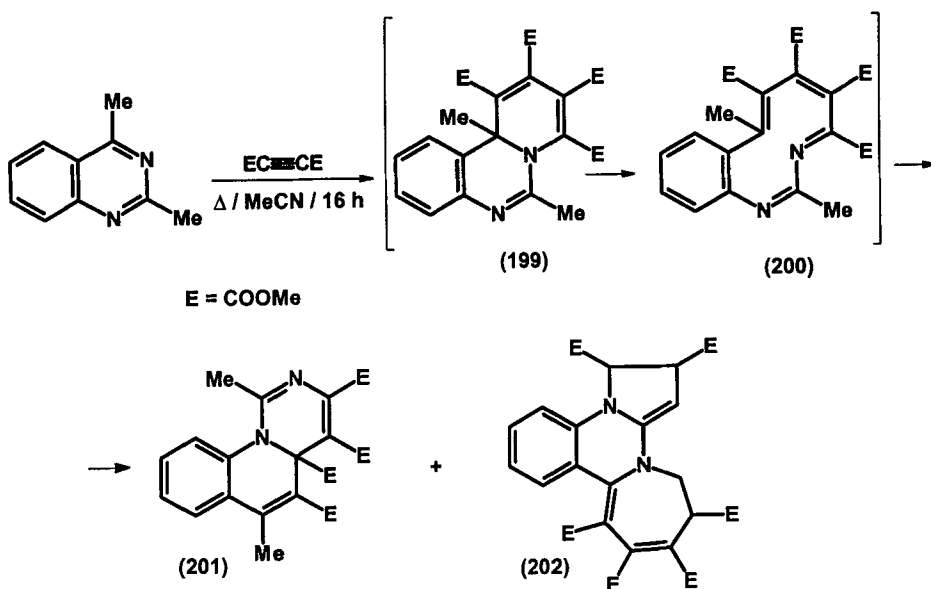
Cycloaddition of 2-(dicyanomethylene)piperidine with iso(thio)cyanates afforded 3-imino-4-cyano-2,3,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidin-1-ones or -1-thiones (**198**, R¹ = H, X = O or S) (78MI1). When excess iso(thio)cyanate was applied, the 3-imino group also reacted to give **198** (R¹ = CXNHR²).

The reaction of ethyl 2-(1,2,3,4-tetrahydroisoquinolin-1-yl)acetate hydrochloride with potassium cyanate in boiling water gave 2,3,4,6,7,11*b*-hexahydro-1*H*-pyrimido[6,1-*a*]isoquinoline-2,4-dione (69IJC684). 3,4,6,7-Tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-2,4-dione and its 2-thioxo derivative were prepared in the reactions of 1-methyl-3,4-dihydroisoquinoline with benzoyl isocyanate and ethoxycarbonyl isothiocyanate, respectively, in the presence of NEt_3 (75CB1541).

Cyclocondensation of 2-(arylamino)quinolines with bis-(2,4,6-trichlorophenyl) 2-substituted malonates at 200–250°C afforded 2-aryl-4-substituted 2,3-dihydro-1*H*-pyrimido[1,6-*a*]quinoline-1,3-diones (83M227).

7. By Formation of Three Bonds from [2+2+2] Atom Fragments

The reaction of 2,4-dimethylquinazoline and dimethyl acetylenedicarboxylate gave the 1:2 and 1:3 adducts **201** and **202** [68JCS(C)926]. It was suggested that pyrimido[1,6-*a*]quinoline (**201**) was produced from the initially formed pyrido[1,2-*c*]quinazoline (**199**) via the 10-membered system **200**.



8. By Formation of Three Bonds from [3+2+1] Atom Fragments

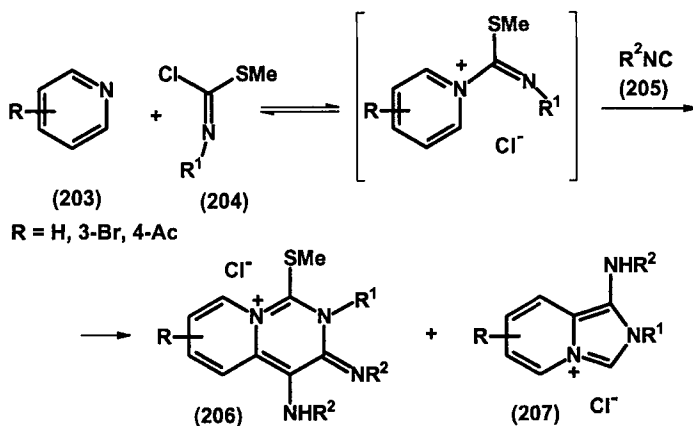
The reaction of 2-(2-phenethyl)quinoline with 2 mol phenyl isocyanate at 180°C for 2 h gave 4-benzyl-2-phenyl-2,3-dihydro-1*H*-pyrimido[1,6-*a*]quinoline-1,3-dione (83M227).

9. By Formation of Four Bonds from [3+1+1+1] Atom Fragments

1-Cyanomethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline reacted with 2 mol formaldehyde and 1 mol primary amines, hydroxylamine, or acylhydrazide to give 3-substituted 1-cyano-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolines (73JHC435; 81CB61; 84MI3). *cis*-1,11*b*-*H*-1-Phenyl-3-substituted 2,3,4,6,7,11*b*-hexahydro-1*H*-pyrimido[6,1-*a*]isoquinolines were prepared in the reaction of 1-benzyl-3,4-dihydroisoquinoline, primary amines, and 2 mol formaldehyde followed by treatment with sodium borohydride (93PHA941; 95MIP3).

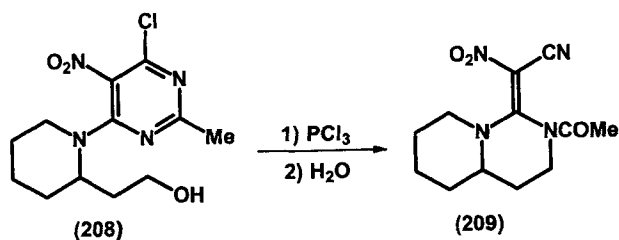
10. By Formation of Four Bonds from [2+2+1+1] Atom Fragments

From the reaction mixtures of pyridines (203) and imidoyl chlorides (204) in the presence of a large excess of isonitriles (205), the pyrido[1,2-*c*]pyrimidium chlorides (206) and the imidazo[1,5-*a*]pyridinium salts (207) could be isolated (93TL2319). The yields of 206 were higher when R¹ and R² were isopropyl groups.

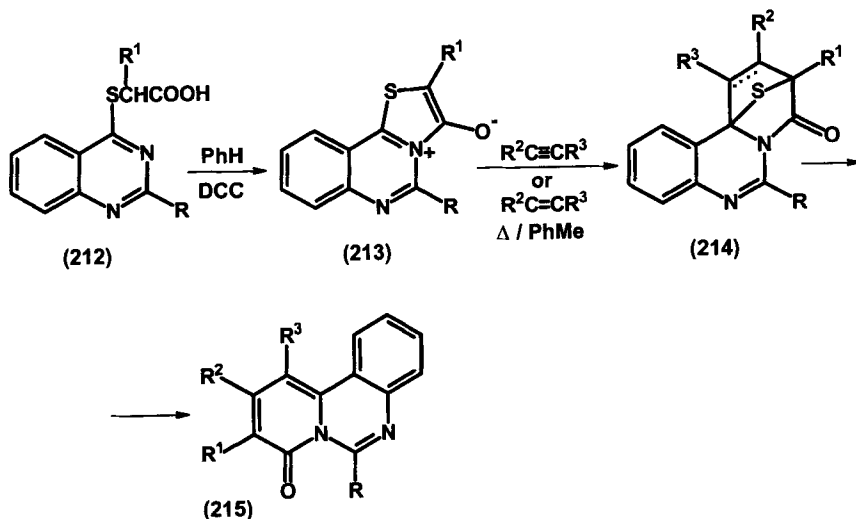
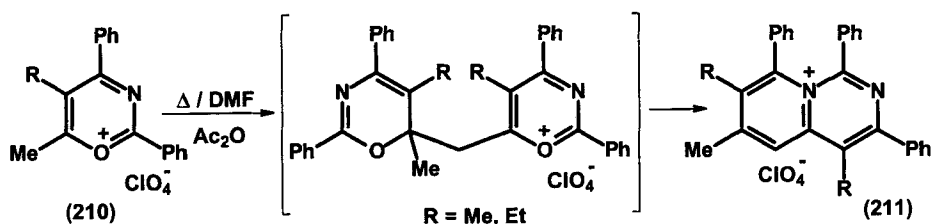


11. Ring Transformations

Treatment of 4-(2-hydroxyethylpiperido)pyrimidine (208) with PCl₃ and then with H₂O yielded 2-acetylpyrido[1,2-*c*]pyrimidine (209) [74JCS(P1)1611].

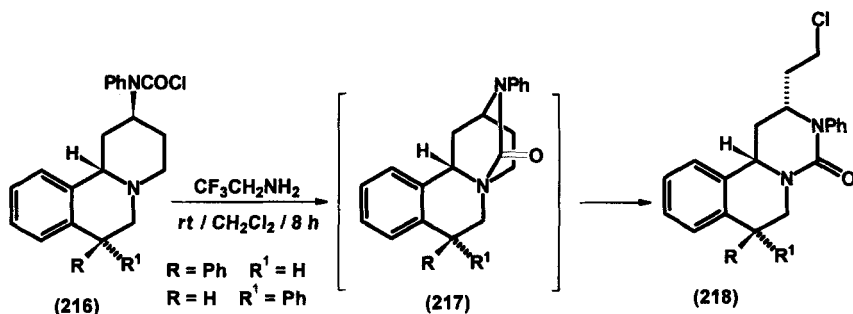


When 1,3-oxazin-4-ium perchlorates (**210**) were heated in DMF in the presence of Ac_2O , pyrido[1,2-*c*]pyrimidin-4-ium perchlorates (**211**) were formed (91KGS1556).

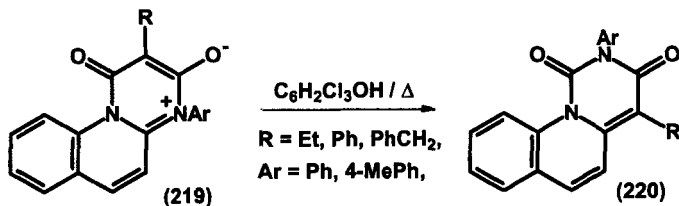


8*H*-Pyrido[1,2-*c*]quinazolin-8-ones (**215**) were obtained from the cycloadducts (**214**) of *anhydro* 3-hydroxythiazolo[3,2-*c*]quinazolin-4-ium hydroxides (**213**) and alkynic (dimethyl acetylenedicarboxylate and ethyl propiolate) and alkenic dipolarophiles (fumaronitrile and methyl vinyl ketone) by extrusion of S or H_2S (85JOC1666). A better yield could sometimes be

achieved when quinoxalines (**212**) were cyclized to **215** in the presence of a dipolarophile.



The regiospecificity of the rearrangement of benzo[*a*]quinolizidines (**216**) to pyrimido[6,1-*a*]isoquinolin-4-ones (**218**) via tetracyclic intermediates (**217**) on the action of 2,2,2-trifluoroethylamine is governed by stereoelectronic factors (82TL2829; 83JOC5074; 84USP4454319). Although triethylamine gave the same products, no reaction occurred with pyridine and dimethylaniline.



The hydrogenation of 1-[(1,2,4-oxadiazol-3-yl)methyl]-6,7-dialkoxy-3,4-dihydroisoquinolines over Pd/C or Raney Ni in acidified ethanol gave hydrochloride salts of pyrido[6,1-*a*]isoquinoline monohydrates (**51**) (86MI1; 87CB1039).

Ring transformation of mesoionic pyrimido[1,2-*a*]quinoline-1,3-diones (**219**) in 2,4,6-trichlorophenole at 240°C afforded pyrimido[1,6-*a*]quinoline-1,3-diones (**220**) (83M227).

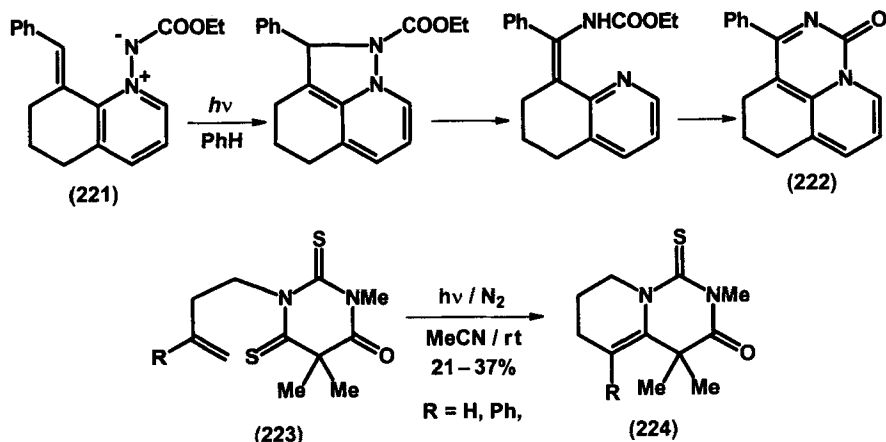
1,3-Dimethyl-6,7,8,9-tetrahydropyrido[1,2-*c*]pyrimidin-4-carboxylate was obtained by both the photochemical rearrangement of 2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in acetic acid (83TL5237; 87JOC2455) and the acidic hydrolysis of 7-(aminoethylidene)-6-methoxy-8-oxo-1-azabicycl[4.2.0]octane in a mixture of benzene and acetic acid (87JOC2455).

The reactions of 1-[(6-methyl-5-methylthio-4-oxo-4*H*-1,3-oxazin-2-yl)-methylene]1,2-dihydroisoquinoline with secondary amines or with ethanolic

KOH furnished 2-amino- and 2-hydroxy-4*H*-pyrimido[6,1-*a*]isoquinolin-4-ones (80YZ1261).

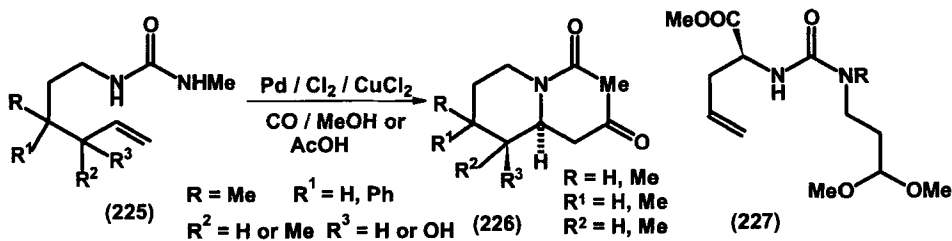
Photochemical transformation of the cycloalkane-annulated pyridinium-*N*-aminide **221** afforded pyrido[3,2,1-*ij*]quinazolin-3-one **222** (88CB411). Photolysis of thiobarbiturates (**223**) gave 1-thioxo-3-oxo-hexahydropyrido[1,2-*c*]pyrimidines (**224**) [96H(42)117].

The reader is also referred here to Section III,A,5.



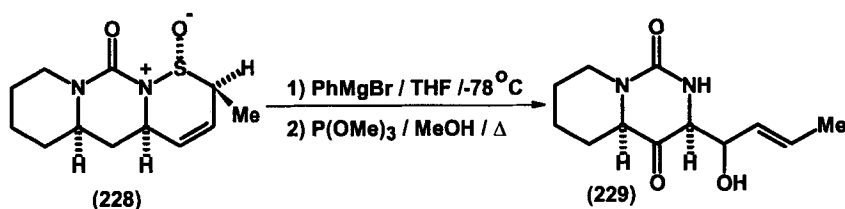
12. Miscellaneous

From the reaction products of the palladium(II)-catalyzed aminocarbonylation of unsaturated ureas (**225**), perhydropyrido[1,2-*c*]pyrimidine-1,3-diones (**226**) could be isolated, among other substances (88JA3994, 88JOC5731). Treatment of **227** with trifluoroacetic acid in methylene chloride at ambient temperature for 2 h afforded 1-oxoperhydropyrido[1,2-*c*]pyrimidine-8-carboxylates (**137**) (96JMC1872).

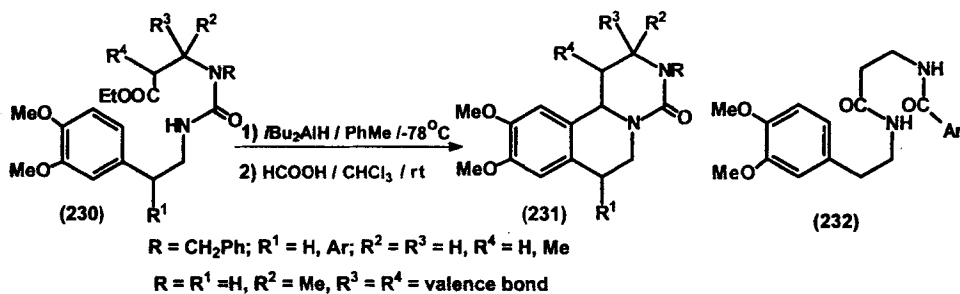


Treatment of tricyclic compound (**228**) with phenylmagnesium bromide gave an allylic sulfoxide, which underwent a stereospecific [2,3]-sigmatropic

rearrangement yielding perhydropyrido[1,2-*c*]pyrimidin-1-one (**229**) (93SL551).



Ureas **230** were cyclized to 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-ones **231** on the action of diisobutylaluminium hydride followed by treatment with formic acid [84S1071; 85H(23)2907]. From **230** ($R = R^1 = H$, $R^2 = Me$, $R^3 = R^4 = \text{valence bond}$), a diastereomeric mixture of **231** ($R = R^1 = R^4 = H$, $R^2 = H$, Me , $R^3 = Me$, H) was obtained (84S1071). Cyclization of carboxamides (**232**) in boiling POCl₃ resulted in 4-aryl-9,10-dimethoxy-6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinolines (51JPJ1007; 55JPJ709, 55CPB253; 61MI1; 63YZ1043).



From the incubated reaction mixture of benzylamine and butyraldehyde or 2-ethyl-2-hexenal in the presence of dissolved oxygen in a mixture of 90% methanol 0.1 *M* phosphate buffer at 37°C for 48 h, 2-benzyl-1-phenyl-6-propyl-4,5,7-triethyl-2,3,5,6,7,8- and -2,4*a*,5,6,7,8-hexahydro-1*H*-pyrido[1,2-*c*]pyrimidines could be isolated (89MI2).

V. Applications and Important Compounds

A. PYRIDO[1,2-*c*][1,3]OXAZINES AND THEIR BENZO DERIVATIVES

Pyrido[1,2-*c*][1,3]oxazines are used as intermediates in the total syntheses of anhydrocannabisativene (84JA3240), (+)-4-hydroxysedamine and (+)-

4-hydroxyallosedamine (85T2891), (–)-3-hydroxyallosedamine (87T935), (±)-lupinine [90H(30)885], (±)-sedridine (91TL4371), (–)-sedamine (93JOC5035), (–)-porantheridine (93JA8851), and (–)-sedacryptine (96SL100)alkaloids. Pyrido[1,2-*c*][1,3]oxazines were often applied to justify the stereochemistry of 2-(2-hydroxyalkyl)piperidines [56CLY1180; 68T4423; 71T2055; 78TL4647; 83H(20)601; 85H(23)831; 88TL1691; 89TL1947; 91T3805; 95TA2149]. [1,3]Oxazino[3,4-*a*]quinolines were used in the stereoselective synthesis of (±)-perhydrogephyrotoxin alkaloid [80JA1454; 84JCS(CC)597; 84TL3247; 86CPB2380].

CNS activities of *trans*-4,4a-H-1-imino-4-phenylperhydropyrido[1,2-*c*][1,3]oxazine were investigated (80MI1). Antitumor activity of 11-methoxy-1,2,4,6,7,11*b*-hexahydro[1,3]oxazino[4,3-*a*]isoquinoline was investigated [94JAP(K)94/41142, 94T6259]. 1[4-(Hexadecyloxy)phenyl]perhydropyrido[1,2-*c*][1,3]oxazine was patented as fading prevention compound for colored photographic material [88JAP(K)88/149643]. 1-Isopropylidene-4,4-dimethyl-1,3,4,4a-tetrahydro[1,3]oxazino[3,4-*a*]quinolin-3-one was investigated as an antiplasticizer for biphenol polycarbonates and was patented as a stiffening agent (66MI1; 67MI1; 68USP3386935; 71USP3625877).

9-Fluoro-10-(cyclic amino)-7-oxo-1*H*,3*H*,7*H*-pyrido[3,2,1-*ij*][3,1]benzoxazine-6-carboxylic acids exhibit antibacterial activities (90EUP373531). The dopaminergic (D2) and serotonergic (5HT_{1A}) activities of 6-(di-*n*-propylamino)-6,7-dihydro-1*H*,3*H*,5*H*-pyrido[3,2,1-*ij*][3,1]benzoxazin-3-one were measured (92JMC1076; 93MI4).

B. PYRIDO[1,2-*c*][1,3]THIAZINES AND THEIR BENZO DERIVATIVES

Certain types of 1-(substituted imino)-1,3,4,4a,5,10-hexahydro[1,3]thiazino[3,4-*b*]isoquinolines, 1-hydroxymethyl-1,2,4,6,7,11*b*-hexahydro[1,3]thiazino[4,3-*a*]isoquinoline-4-(thi)ones, and 1,5,6,7-tetrahydro-3*H*-pyrido[3,2,1-*ij*][3,1]benzothiazine-3-(thi)ones are patented as analgesics, anti-inflammatories, and antipyretics (79GEP2848926; 80GEP3017865; 85GEP3510526) and as agrochemical fungicides [87EUP239927; 88JAP(K)88/170385].

C. PYRIDO[1,2-*c*]PYRIMIDINE AND THEIR BENZO DERIVATIVES

2-[3-(1,3-Dioxolan-1-yl)propyl]perhydropyrido[1,2-*c*]pyrimidin-3-one was used in the preparation of racemic tetraponerines T4 and T8 alkaloids (90TL4543). Actisomide, an antiarrhythmic agent (**18**), has been introduced into human therapy (85JMC1285; 87MI1; 88MI1). 2-(2-Fluoro-4-chloro-5-

propargyloxy)perhydropyrido[1,2-*c*]pyrimidin-2-one was patented as a protoporphyrinogen oxidase inhibitor (94USP5298502).

1-Aryl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-2,4-diones are useful precursors in the synthesis of the pyrimidoaporphine nucleus (84T4003). 6-(*N,N*-Dipropylamino)-1,2,3,5,6,7-hexahydropyrido[3,2,1-*ij*]-quinazolin-3-one exhibits selective serotonin (5HT_{1A}) agonist activity (92JMC1076; 93JMC1301, 93MI4; 95JMC1295). Representatives of broad-spectrum antibacterials, carbapenems contain 5,6,7,8-tetrahydropyrido[1,2-*c*]pyrimidinium moieties (86EUP168707, 86EUP169410).

Trequinsin (**19**) was under clinical investigation as a very potent antihypertensive peripheral vasodilator having platelet aggregation inhibitory properties (82MI1; 84JMC1470; 87MI3). Trequinsin (**19**) was claimed to be useful in the treatment of alopecia (89GEP3816995; 90EUP370379). Its biological properties were intensively investigated [81MI1; 84MI1, 84MI2, 84MI4; 85JMC1285, 85MI1; 86MI1, 86MI2, 86MI3; 87MI1, 87MI2, 87MI4, 87MI5, 87MI6, 87MI8; 88AF240, 88MI2; 89MI1; 90BJ(266)127, 90MI1, 90MI2; 91MI1, 91MI2, 91MI3; 92JBC(267)1798, 92MI1, 92MI2, 92PHA46; 93MI5; 94JBC30676; 95MI1, 95MI2, 95MI3, 95MIP1, 95MIP2; 96GEP4430128].

2-Dodecyl- and 2-ethylperhydropyrido[1,2-*c*]pyrimidines were patented as fading prevention compounds for colored photographic material [88JAP(K)88/149643].

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Heterocycle-Fused Acridines

PAUL W. GROUNDWATER

*School of Health Sciences, University of Sunderland, Sunderland
SR1 3SD, United Kingdom*

MUNAWAR ALI MUNAWAR

Department of Chemistry, Islamia University, Bahawalpur, Pakistan

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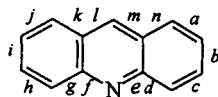
I. Introduction

This review covers the following groups of heterocycle-fused acridines: pyridoacridines, pyranoacridines, pyrroloacridines, thienoacridines, and furoacridines.

Heterocycle-fused acridines possess a variety of biological activities, including Ca^{2+} releasing, antiviral (e.g., anti-HIV), antimicrobial (e.g., antiamebic and antiplasmodium) and antitumor properties. They are also enzyme inhibitors (e.g., topoisomerase II inhibitors and protein tyrosine kinase inhibitors) and have DNA-intercalation and metal-chelating properties.

II. Pyridoacridines

Depending on the ring fusion, pyridoacridines can be classified into the following main classes: pyrido[*a*]acridines (benzo[*j*]phenanthrolines), pyrido[*b*]acridines, pyrido[*c*]acridines (benzo[*b*]phenanthrolines), and pyrido[*kl*]acridines (dibenzo[*f,ij*][2,7]naphthyridines).

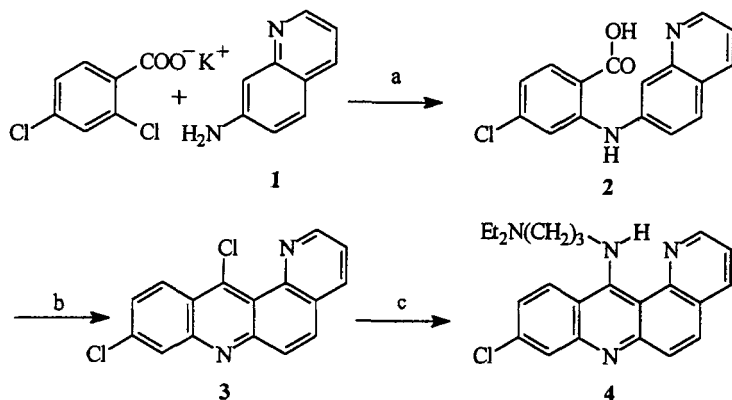


A. PYRIDO[*a*]ACRIDINES (BENZO[*j*]PHENANTHROLINES)

The pyridine ring is fused at bond *a* of the acridine. Depending on the position of the nitrogen in the fused pyridine ring, four different types of pyrido[*a*]acridines are possible.

1. *Pyrido*[2,3-*a*]acridines (*Benzo*[*j*][1,7]phenanthrolines)

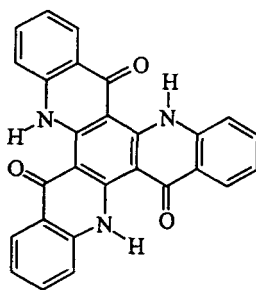
Dobson *et al.* (48JCS123) constructed this ring system by using the Ullmann-amine coupling reaction between 7-aminoquinoline **1** and potassium 2,4-dichlorobenzoate, followed by cyclization of the resultant diaryl-



SCHEME 1. (a) Cu bronze, amyl alcohol, 150°C, 6 h; (b) POCl₃/PCl₅, 150°C, 6 h; (c) diethylaminopropylamine, phenol, 100°C, 2 h.

amine **2** with a mixture of POCl₃ and PCl₅ (Scheme 1). The pyridoacridine **3** was then converted to a potential antimalarial compound **4**, but poor activity was observed.

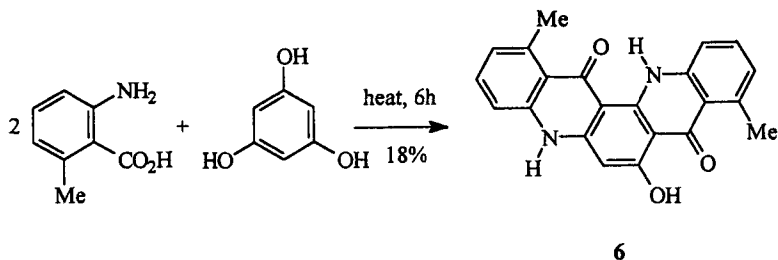
Gordon *et al.* (90MI1) obtained a triquinobenzene **5** from a two-step reaction between 1,3,5-tribromobenzene and anthranilic acid. The reaction involved three Ullmann-amine couplings followed by intramolecular acylations.



5

Reisch *et al.* (93JHC1469) obtained quino[*a*]acridone **6** as the main product from the condensation of phloroglucinol and 6-methylanthranilic acid (Scheme 2). The synthesis of similar quino[*a*]acridones from phloroglucinol and anthranilic acids has been reported in patents (35FRP771486).

The condensation product **7** of *m*-phenylenediamine and 2-formylcyclohexanone, on treatment with polyphosphoric acid (PPA), gave the octahydrobenzophenanthroline **8**, which, on dehydrogenation, afforded



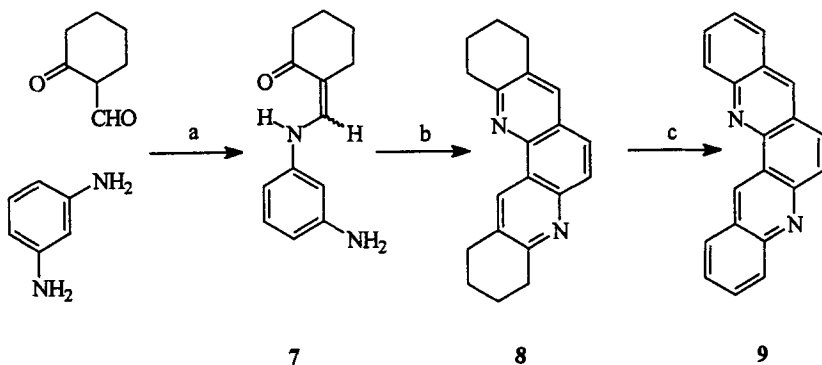
SCHEME 2

quino[*a*]acridine **9** (Scheme 3) (74IJC1230). A rearrangement prior to cyclodehydration is involved. The synthesis of similar compounds from 1,3-diiodobenzene and 2-acylanilines, using the Ullmann-amine coupling reaction followed by cyclization, has been reported by Hellwinkel and Ittemann (85LA1501).

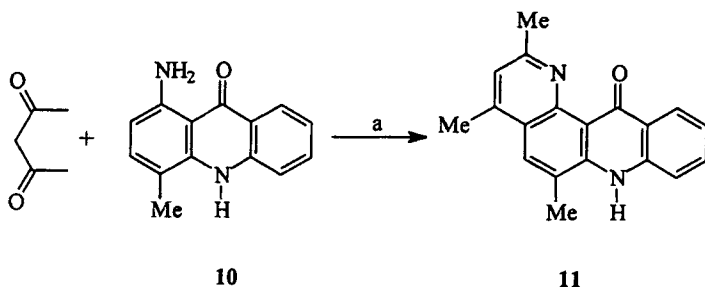
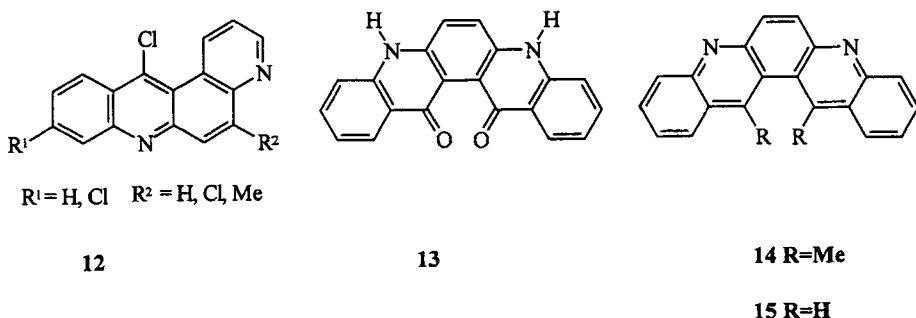
In an attempted reaction toward a pyrido[2,3,4-*kl*]acridine, Gellerman *et al.* (92TL5577) isolated a pyrido[2,3-*a*]acridine **11** from an acid-catalyzed reaction between 1-amino-4-methylacridin-9(10*H*)one **10** and acetylacetone (Scheme 4).

2. Pyrido[3,2-*a*]acridines (Benzo[*j*][4,7]phenanthrolines)

12-Chloropyrido[3,2-*a*]acridines **12** were prepared by the route described in Scheme 1, but with 6-aminoquinolines instead of 7-aminoquinoline (46JCS151; 47JCS678). The chloroderivatives **12** were then converted to potent antimalarial agents with dialkylaminoalkylamines or alkylaminoalkylamines in phenol at 100°C.

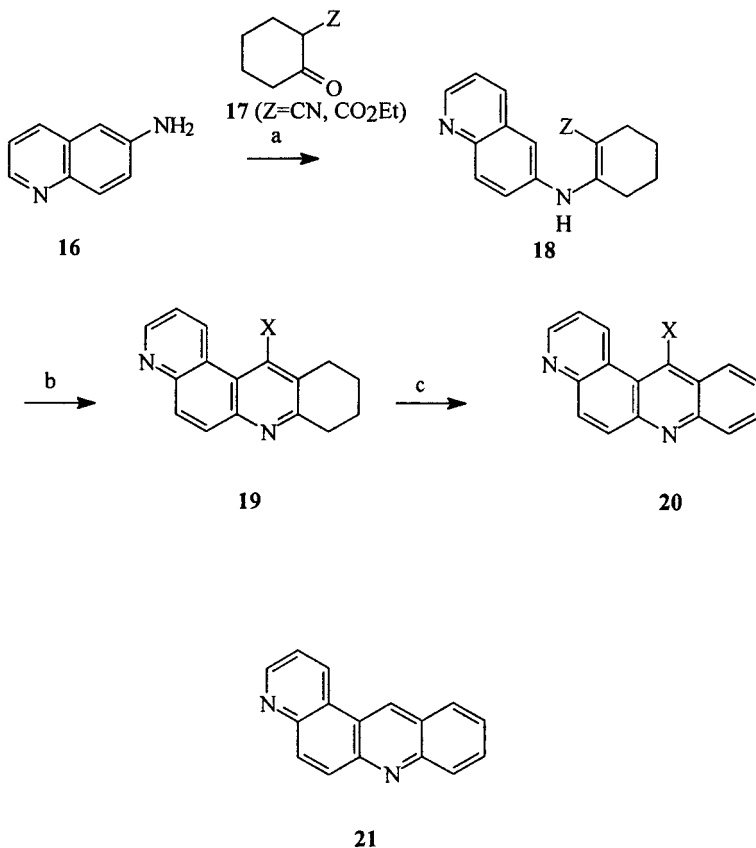


SCHEME 3. (a) EtOH, rt, 65%; (b) PPA, 160–170°C, 2 h, 40%; (c) Se, 300°C, 6 h, 58%.

SCHEME 4. (a) AmOH, H⁺, 130°C, 1.5 h, 40%.

The double Ullmann-amine coupling of *p*-phenylenediamine with 2-chlorobenzoic acid followed by two acid-catalyzed Friedel-Crafts acylations afforded quino[3,2-*a*]acridone **13** (52JCS1874). A similar regioselectivity was observed when 1,4-diiodobenzene was coupled with aminoacetophenone and the resultant diketone was treated with H₂SO₄ to give quino[3,2-*a*]acridine **14** (85LA501). The quino[3,2-*a*]acridine **15** was obtained after dehydrogenation of the minor product from *p*-phenylenediamine and 2-formylcyclohexanone (see Section II,B,1 on pyrido[2,3-*b*]acridines) (74IJC1324).

We have prepared pyrido[3,2-*a*]acridines, **20** and **21** (96TH1), by Lewis acid-catalyzed cyclization of enamines **18**, formed by the condensation of 6-aminoquinoline **16** with 2-cyano-**17a** (Z = CN) or 2-ethoxycarbonylcyclohexanone **17b** (Z = CO₂Et), to give the tetrahydropyrido[2,3-*a*]acridines **19**. Oxidation of these tetrahydro derivatives, with palladium on charcoal, gave the fully aromatic systems **20** (Scheme 5). Oxidation of the amino derivative **19a** also resulted in the formation of some of the deaminated product **21**.

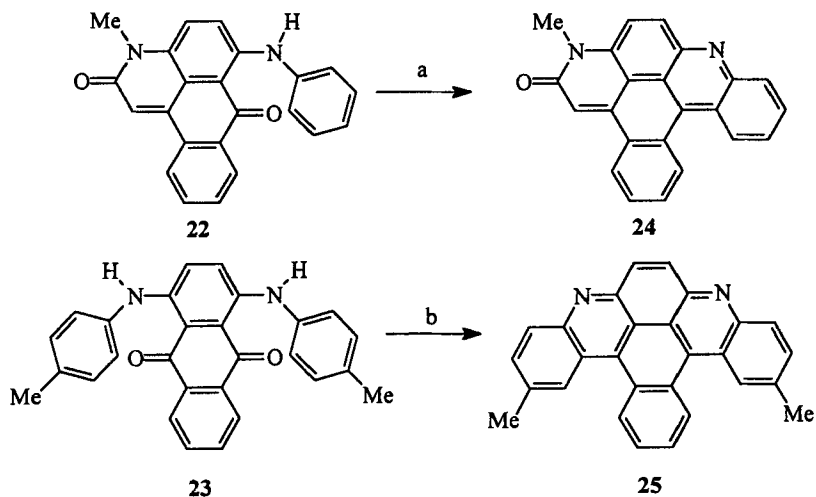


SCHEME 5. **a** X = NH₂, **b** X = OH. (a) PhCH₃, reflux; (b) AlCl₃, 190°C; (c) Pd-on-C, 270–300°C.

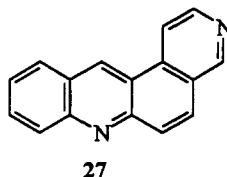
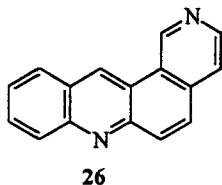
The synthesis of some hexa- and heptacyclic molecules **24** and **25** containing a pyrido[3,2-*a*]acridine nucleus has been reported, the principal step being the ring closure of anthraquinone-derived precursors **22** and **23** (Scheme 6) (84KGS962).

3. Pyrido[3,4-*a*]acridines (Benzo[*j*][2,7]phenanthrolines)

No natural or synthetic compounds based on this ring system **26** have been reported.



SCHEME 6. (a) PPA, 170°C, 96%; (b) PPA, 180°C, 79%.



4. *Pyrido[4,3-a]acridines (Benzo[j][3,7]phenanthrolines)*

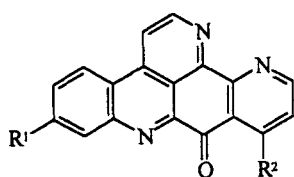
No natural or synthetic compounds based on this ring system **27** have been reported.

B. PYRIDO[*b*]ACRIDINES

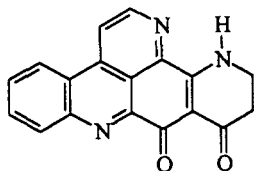
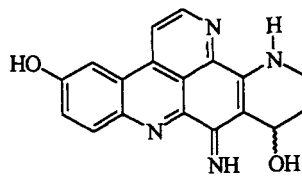
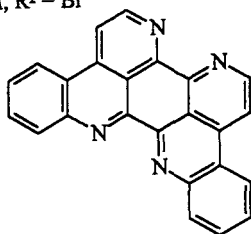
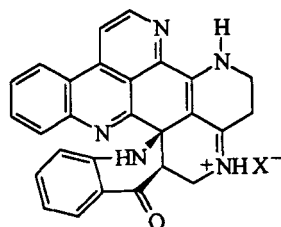
The auxiliary pyridine ring is fused at bond *b* of the acridine nucleus in this class of pyridoacridines and, depending on the position of nitrogen in the auxiliary pyridine, four different types of pyrido[*b*]acridines are possible.

1. *Pyrido[2,3-*b*]acridines*

This ring system can be seen in the pentacyclic alkaloids: ascididemin **28**, 2-bromoleptoclinidone **29**, 11-hydroxyascididemin **30**, 8,9-dihydro-11-hydroxyascididemin **31**, calliactine **32**, the heptacyclic eilatin **33**, and the octacyclic biemnadin **34**. (See Section II,D,1 on pyrido[2,3-*kl*]acridines.)

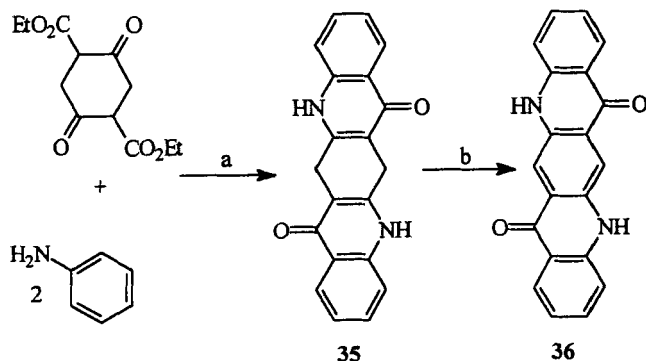


- 28** $R^1 = R^2 = H$
29 $R^1 = Br, R^2 = H$
30 $R^1 = H, R^2 = Br$

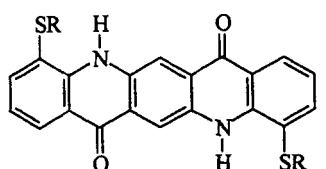
**31****32****33****34**

The organic pigments, the linear-*trans*-quinacridones, such as **36**, also possess this ring system. These quinacridones can be used in printing ink and as a colorant for plastics (67CRV1). They also exhibit photovoltaic and photoconductive properties (84CL1305; 87CL609). A large number of quinacridones have been synthesized. The synthetic methods have been reviewed by Labana and Labana (67CRV1). The most useful method involves the dehydrogenation of dihydroquinones, such as **35**, prepared from diethyl 2,5-dioxo-1,4-cyclohexanedicarboxylate and anilines (Scheme 7).

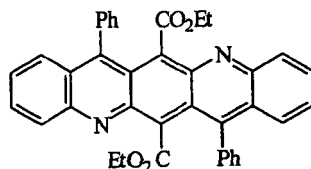
Some soluble quinacridones **37** have been prepared by applying this strategy (92JHC167). The introduction of long alkylthio groups into the 4 and 11 positions weakened the intermolecular hydrogen bonding and increased the solubility in different solvents. Diethyl 2,5-dioxo-1,4-cyclohexanedicarboxylate, on acid-catalyzed condensation with 2-aminobenzophenone followed by dehydrogenation with chloranil, afforded quinacridine **38** (88JHC1063).



SCHEME 7. (a) Heat; (b) e.g., chloranil.



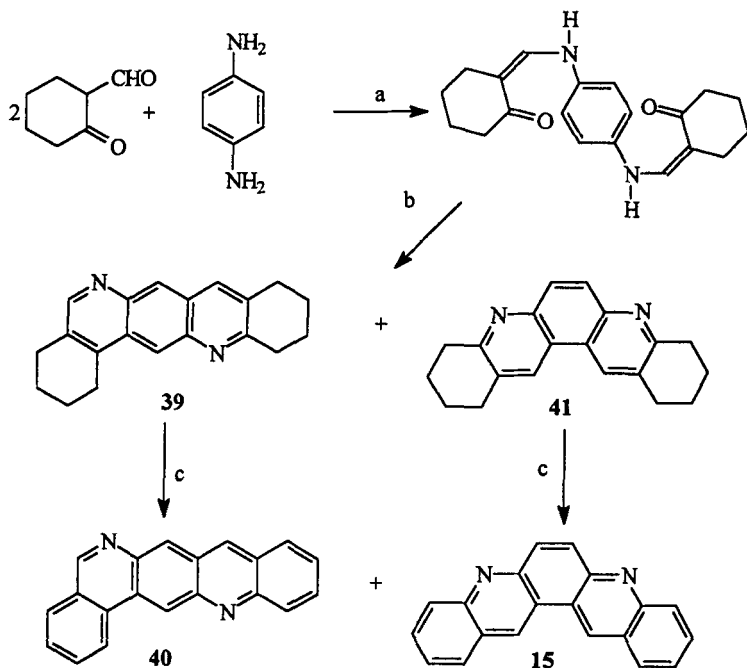
R = C₆H₁₃, C₈H₁₇, C₁₀H₂₁, C₁₂H₂₅

37**38**

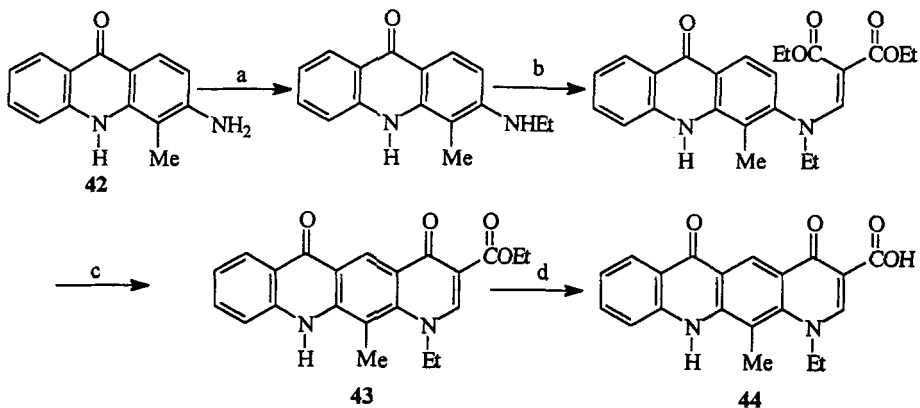
The synthesis of isoquino[3,4-*b*]acridine **40** from the interaction of *p*-phenylenediamine with 2-formylcyclohexanone, followed by ring closure (after *in situ* rearrangement) and then dehydrogenation of **39**, has been reported by Berde *et al.* (72IJC332). Further examination of the cyclodehydration reaction also gave octahydroquino[3,2-*a*]acridine **41** as the minor product, which was then dehydrogenated to provide quino[3,2-*a*]acridine **15** (Scheme 8) (74IJC1324).

2. Pyrido[3,2-*b*]acridines

Morton *et al.* (93H2757) have described a synthesis of pyrido[3,2-*b*]acridones **43** and **44** starting from 3-amino-4-methylacridin-9(10*H*)one **42** (Scheme 9). Both compounds were found to be inactive against cultured



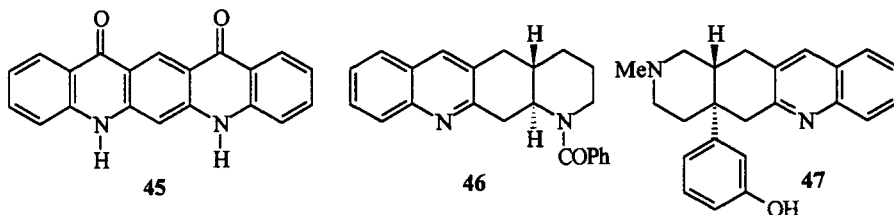
SCHEME 8. (a) EtOH, rt, 77%; (b) PPA, 180°C, 3 h, 51% (**39**), 14% (**41**); (c) Se, 300–330°C, 5–10 h, 25% (**40**), 38% (**15**).



SCHEME 9. (a) NaBH₄, AcOH, 10 h, 75%; (b) EtOCH=C(CO₂Et)₂, 155–160°C, 1.5 h.; (c) PPE, 120–125°C, 1.5 h, 72% (b,c); (d) NaOH, EtOH, 2 h, 67.5%.

L1210 cells at concentrations up to $10\ \mu\text{M}$ and showed negligible antibacterial activity.

The acid-catalyzed conversion of *N,N'*-bis(2'-carboxyphenyl)-1,3-diaminobenzene to quino[3,2-*b*]acridone **45** has been described in a patent (64USP3124581). Kumar and Jain [79IJC(B)623] have reported the synthesis of the octahydroquinolino[*b*]quinoline **46** from the base-catalyzed condensation of *N*-benzoyldecahydroquinolin-7-one with 2-aminobenzaldehyde.

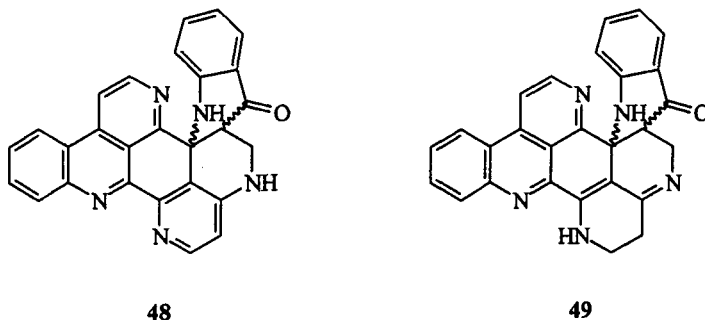


3. Pyrido[3,4-*b*]acridines

The synthesis of decahydropyrido[3,4-*b*]acridine **47**, by a Friedländer reaction, and its opioid-antagonistic activity ($\text{IC}_{50} = 54\ \text{nM}$) has been claimed [92JAP(K)92/275288].

4. Pyrido[4,3-*b*]acridines

Pyridoacridine alkaloids, eudistone A **48** and B **49**, possess this ring as a part of their structures (see pyrido[2,3,4-*kl*]acridines).

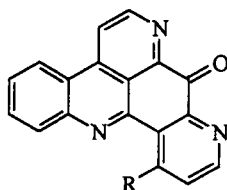


C. PYRIDO[*c*]ACRIDINES (BENZO[*b*]PHENANTHROLINES)

The auxiliary pyridine is fused at bond *c* of the acridine nucleus. Depending upon the position of the nitrogen in the auxiliary pyridine ring, four different types of pyrido[*c*]acridine are possible.

1. Pyrido[2,3-*c*]acridines (Benzo[*b*][1,7]phenanthrolines)

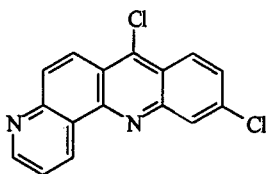
Among the pyridoacridine alkaloids, meridine **50** and cystodamine **51** exhibit this ring skeleton (see Section II,D,1 on pyrido[2,3,4-*k*l]acridines). This ring pattern can also be observed in quino[*a*]acridines **6** and **9** and triquinobenzene **5** (see Section II,A,1 on pyrido[2,3-*a*]acridines).



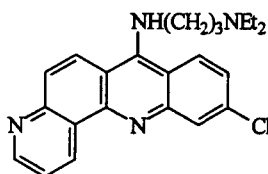
50 R = OH

51 R = NH₂

In search of potential anti-malarial agents, Dobson *et al.* (48JCS123) prepared 7,10-dichlorobenzo[*b*][1,7]phenanthroline **52** by the route described in Scheme 1, but with 5-aminoquinoline **48** as a precursor of 7-diethylaminopropylamino-10-chlorobenzo[*b*][1,7]phenanthroline **53**. No significant activity was observed when compound **53** was tested against *Plasmodium gallinaceum* (*in vivo*).



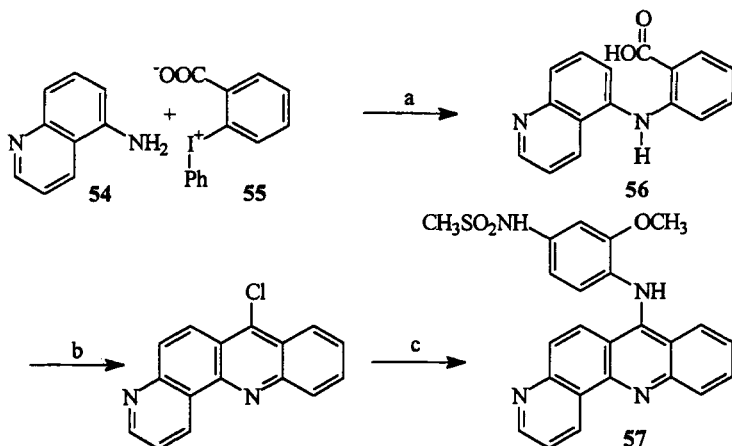
52



53

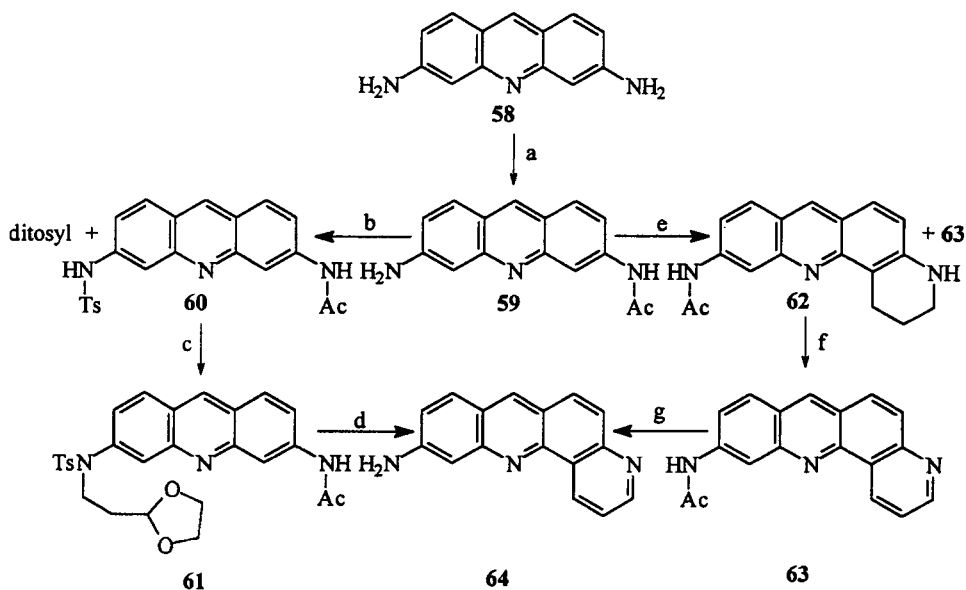
The coupling reaction between 5-aminoquinoline **54** and 2-chlorobenzoic acid gave a very poor yield (5%) of quinolyanthranilic acid **56**. With diphenyliodonium-2-carboxylate **55**, the yield increased to 80%. Quinolyanthranilic acid **56** was then converted to the sulfonamide **57** after cyclization with POCl₃ (Scheme 10) (87MI1). The sulfonamide **57** showed negligible activity against L1210 leukemia cells in culture, against P388 leukemia *in vivo*, and against the Lewis lung solid tumor.

Wardani and Lhomme (93TL6411) reported two routes for the synthesis of 10-aminobenzo[*b*][1,7]phenanthroline **64** from 3,6-diaminoacridine (proflavine) **58**. In first route the proflavine **58** was monoacylated to give **59**. Activation of the free amino group was achieved by tosylation. Alkylation of the monoacetyl monotosyl proflavine **60** with 3-bromopropionaldehyde ethylene acetal gave the intermediate **61**. Acidic treatment afforded 10-aminobenzo[*b*][1,7]phenanthroline **64** in an 18% overall yield starting from



SCHEME 10. (a) Cu^{2+} (CH_3COO^-)₂, *N*-methylpyrrolidone, 95°C, 12 h, 80%; (b) POCl_3 , Δ ; (c) 4-amino-3-methoxymethanesulfonanilide, H^+ , MeOH.

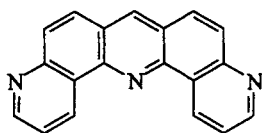
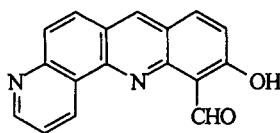
proflavine **58** (Scheme 11). The second route involves the Skraup cyclization. The monoacylated proflavine **59** was reacted with acrolein diethyl acetal in refluxing acetic acid. The resultant mixture of **62** and **63** was treated



SCHEME 11. (a) Ac_2O , EtCO_2H , 20°C, 10 h, 83%; (b) TsCl , pyridine, Et_3N , 4°C, 10 h, 65% (**60**); (c) DMF , K_2CO_3 , $\text{BrCH}_2\text{CH}_2\text{CH}(\text{OCH}_2)_2$, 80°C, 3 h, 72%; (d) H_2SO_4 , 1 h, 40%; (e) AcOH , $\text{CH}_2=\text{CHCH}_2\text{CH}(\text{OC}_2\text{H}_5)_2$, reflux, 3 h; (f) DDQ , AcOH , 100°C, 15 min.; (g) 4 *M* HCl , 80°C, 1 h, 40% (e,f,g).

with DDQ in acetic acid to afford **63** as the sole product. Deprotection with 4 M HCl produced 10-aminobenzo[*b*][1,7]phenanthroline **64** (Scheme 11). The Skraup synthesis of dipyridoacridine **65** from proflavine **58** has also been reported [67JCS(C)1415].

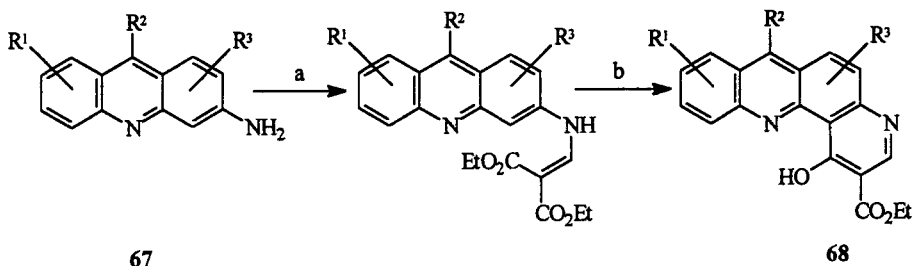
The synthesis of a number of benzo[*b*][1,7]phenanthroline anticancer agents from 10-aminobenzo[*b*][1,7]phenanthroline **64** has been claimed (91MIP1). Thus, 11-formyl-10-hydroxybenzo[*b*][1,7]phenanthroline **66** exhibited cytotoxicity, with an IC_{50} of 6.5 μM , against L1210 leukemia cells.

**65****66**

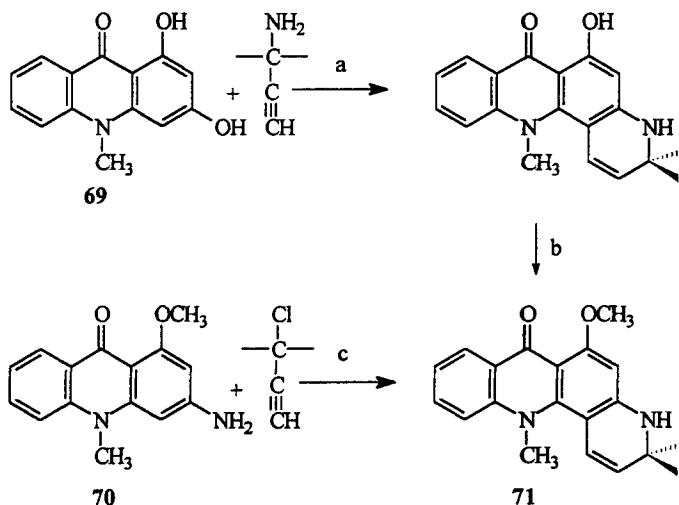
A large number of 1-hydroxy-2-ethoxycarbonylbenzo[*b*][1,7]phenanthrolines **68** have been synthesized from 3-aminoacridines **67** by using the route shown in Scheme 12, and potent antimicrobial activities and low toxicities have been claimed (78USP4060527).

Reisch *et al.* (93JHC981) described two different methods for the synthesis of 4-azaacronycine **71**. One method involves the fusion of 1,3-dihydroxy-10-methyl-9(10*H*)-acridone **69** with 3-amino-3-methylbut-1-yne in the presence of $CuCl_2$ in a closed ampule, followed by methylation (Scheme 13). The second method involves the *N*-alkylation of 3-amino-1-methoxy-10-methyl-9(10*H*)-acridone **70** with 3-chloro-3-methylbut-1-yne, followed by *in situ* cyclization (Scheme 13).

We prepared a range of pyrido[2,3-*c*]acridines **74** by the base- or acid-catalyzed cyclization of the corresponding enamines **72**, followed by



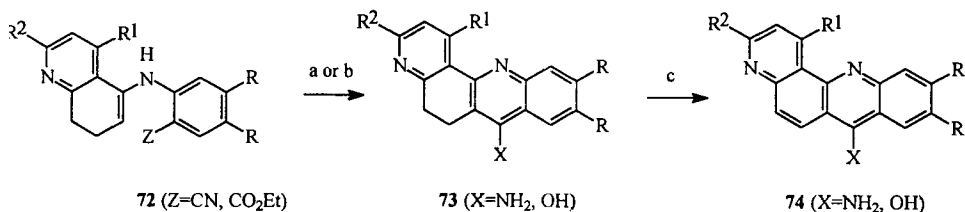
SCHEME 12. $R^1, R^2, R^3 = H, \text{alkyl, aryl, alkylamino, alkylthio, nitro, cyano, alkylsulfonyl, etc.}$ (a) $EtOCH=C(CO_2Et)_2, \Delta$; (b) $Ph_2O, 260^\circ C$.



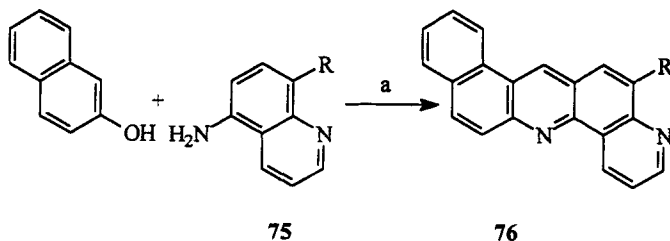
SCHEME 13. (a) CuCl_2 , heat, closed ampule; (b) methylation, 10% (a,b); (c) DMF, K_2CO_3 , KI, 120°C , 8 h, N_2 , 20%.

oxidation of the dihydro derivatives **73** (Scheme 14) (96TH1). The aminopyrido[2,3-*c*]acridine **74a** was tested for the inhibition of the spontaneous proliferation of a human gastric carcinoma cell line, MKN 45, and had an $\text{IC}_{50} < 1 \mu\text{mol dm}^{-3}$, but was noncytotoxic (95BRP9425409, 95MIP1).

Buu-Hoï [67JCS(C)213] used a quite different method for the construction of the benzo[*b*][1,7]phenanthroline ring system. Condensation of 2-naphthol with 5-aminoquinolines **75** and paraformaldehyde generated naphthaleno[*b*][1,7]-phenanthrolines **76** (Scheme 15).



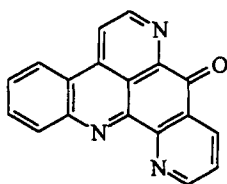
SCHEME 14. $\text{R} = \text{H}$ or OMe , $\text{R}^1 = \text{H}$ or OH , $\text{R}^2 = \text{H}$ or OH . (a) NaNH_2 , DME, reflux, 3 h; (b) H_3PO_4 , $150\text{--}160^\circ\text{C}$; (c) MnO_2 , DMF, reflux.



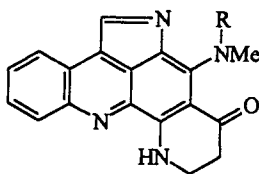
SCHEME 15. (a) Paraformaldehyde, 250°C, 17% (R = H), 43% (R = Me).

2. Pyrido[3,2-*c*]acridines (Benzo[*b*][1,10]phenanthrolines)

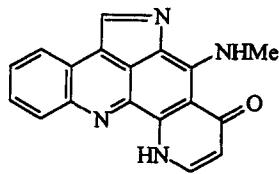
Eilatin **33** and eudistone A **48** and B **49** are pyridoacridine alkaloids that possess this ring skeleton. This ring system is also found in a synthetic isomer, isoascidemin **77**, of ascididemin **28** (see pyrido[*b*]acridines and pyrido[2,3,4-*kl*]acridines). Three other alkaloids, the plakinidines (A–C) **78–80** from *Plakortis* sponge, also share this ring system (90JA1, 90TL3271).



77



78 R = H

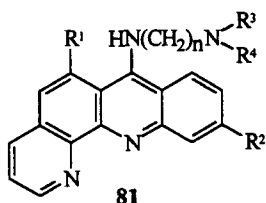


80

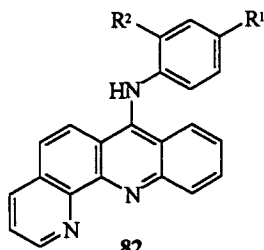
79 R = Me

The synthesis of a number of 7-(mono and dialkylaminoalkylamino) derivatives **81** (46JCS151; 47JA1543; 62JMC546; 72JMC739), and 7-anilino derivatives **82** (87MI1; 93JPS262) of benzo[*b*][1,10]phenanthrolines by the route described in Scheme 1, but using 8-aminoquinolines instead of 7-aminoquinoline, and their biological evaluation has been reported. Benzo[*b*][1,10]phenanthroline-7-ones **83** were also separated during these syntheses. Some of the alkylamino derivatives **81** were found to be highly effective against ascites tumors at low dosage (72JMC739). The anilino derivatives **82** were found to be active against L1210 murine leukemia (93JPS262), P388 leukemia cells (87MI1), and a Lewis lung solid tumor (87MI1). Using the same strategy, Wilkinson and Finar (48JCS288) have prepared some 7-aminobenzo[*b*][1,10]phenanthrolines **84** and related compounds. None of the amino derivatives showed significant antibacterial or

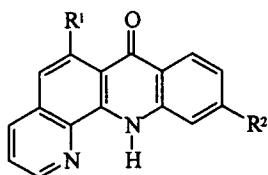
trypanocidal activity. The same route was used to prepare 7-dimethylamino-propylthiobenzo[*b*][1,10]phenanthroline **85** as a potential platelet aggregation inhibitor (72JMC61). No significant activity was observed.

**81**

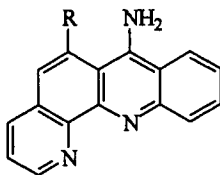
$R^1 = \text{H, OMe}; R^2 = \text{H, Cl}$
 $R^3 = \text{H, alkyl, chloroalkyl, etc.}$
 $R^4 = \text{alkyl, chloroalkyl, etc.}$

**82**

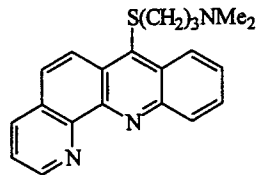
$R^1 = \text{H, Me}_2\text{N, MeSO}_2\text{NH, PhSO}_2\text{NH}$
 $R^2 = \text{H, MeO, MeNH, Me}_2\text{N}$

**83**

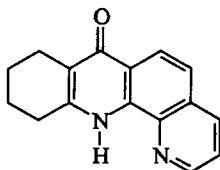
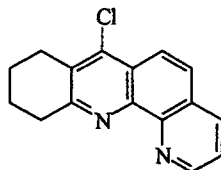
$R^1 = \text{H, MeO}; R^2 = \text{H, Cl}$

**84**

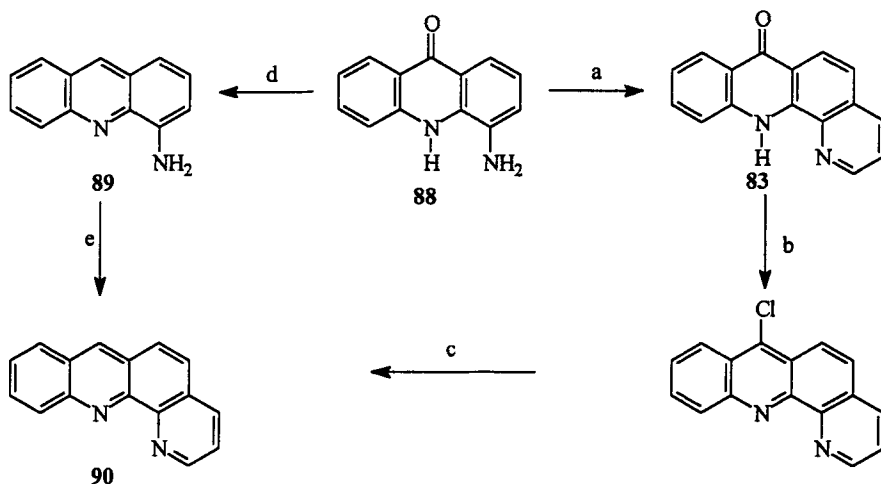
$R = \text{H, F, MeO}$

**85**

The synthesis and antileishmania activity of 8,9,10,11-tetrahydrobenzo[*b*][1,10]phenanthroline-7(12*H*)-one **86** and 7-chloro-8,9,10,11-tetrahydrobenzo[*b*][1,10]phenanthroline **87** has been described by Satti *et al.* [93-IJC(B)978].

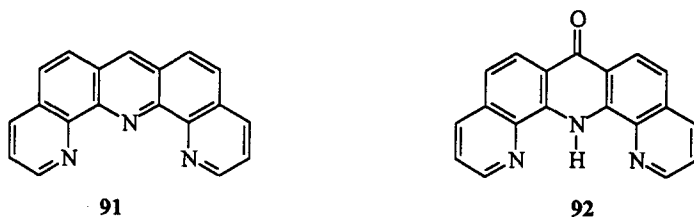
**86****87**

A quite different approach to the construction of the benzo[*b*][1,10]-phenanthroline ring system, for example, **90**, was used by Koft and Case

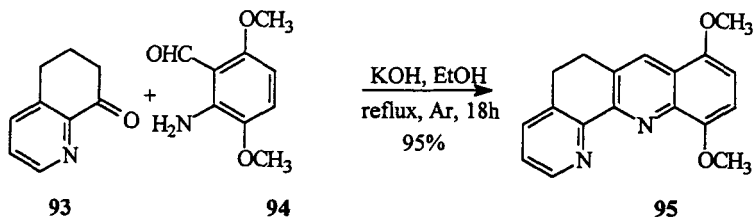


SCHEME 16. (a) $\text{HOCH}(\text{CH}_2\text{OH})_2$, H_3AsO_4 , H_2SO_4 , H_2O , $130\text{--}140^\circ\text{C}$, 2.5 h, 53%; (b) $\text{POCl}_3/\text{PCl}_5$, reflux, 5 h, 81%; (c) 10% Pd on charcoal, H_2 , EtOH, KOH, 3 h, 36%; (d) Na-Hg, EtOH, H_2O , NaHCO_3 , 4–5 h, 47%; (e) $\text{H}_2\text{C}=\text{CHCHO}$, H_3AsO_4 , H_3PO_4 , $100\text{--}110^\circ\text{C}$, 1 h, 8.5%.

(62JOC865). They used 4-aminoacridone **88** and 4-aminoacridine **89** as the starting materials (Scheme 16). The Skraup synthesis was also applied to the preparation of quino[8,7-*b*][1,10]phenanthroline **91** and its 7-oxo derivative **92** (62JOC865).

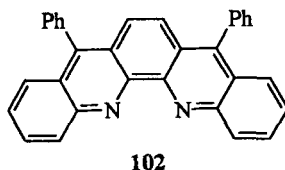


Condensation of 5,6-dihydroquinolin-8(7*H*)-ones, such as **93**, with 2-aminoaromatic aldehydes, such as **94**, afforded dihydrobenzo[*b*][1,10]phenanthrolines, such as **95** (Scheme 17), as precursors of a number of interesting compounds (88JA3673; 90AGE923; 93JOC1666). Condensation of 5,6-dihydroquinolin-8(7*H*)-one **93** with ternary iminium perchlorates, for example, **96**, in the presence of ammonium acetate has been reported to give compounds such as **97** that contain the benzo[*b*][1,10]phenanthroline ring system (Scheme 18) (93TL1775).

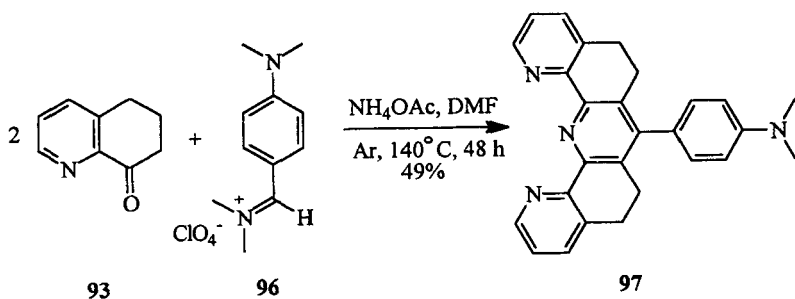


SCHEME 17

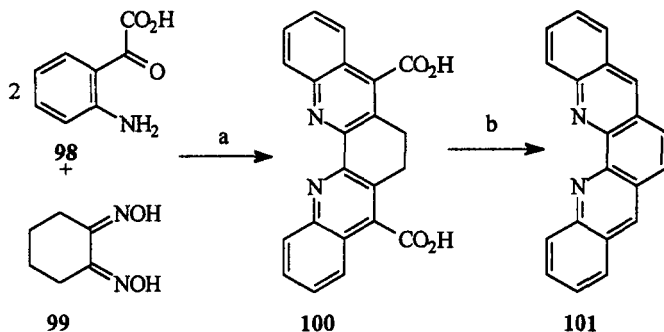
Cyclocondensation of 2-aminobenzoylformic acid **98** and cyclohexane-1,2-dione dioxime **99**, followed by decarboxylation with concomitant dehydrogenation of the diacid **100**, gave quino[3,2-*c*]acridine **101** (70JPR1105). The same skeleton **102** was obtained from the Ullmann-amine coupling reaction of 2-aminobenzophenone and 1,2-diiodobenzene, followed by ring closure (85LA1501).



In a search for dyestuffs, *o*-phenylenediamine was reacted with 1-nitroanthraquinone and the resulting bisquinone **103** was cyclized with H_2SO_4 to give **104** (Scheme 20) (74MI1).



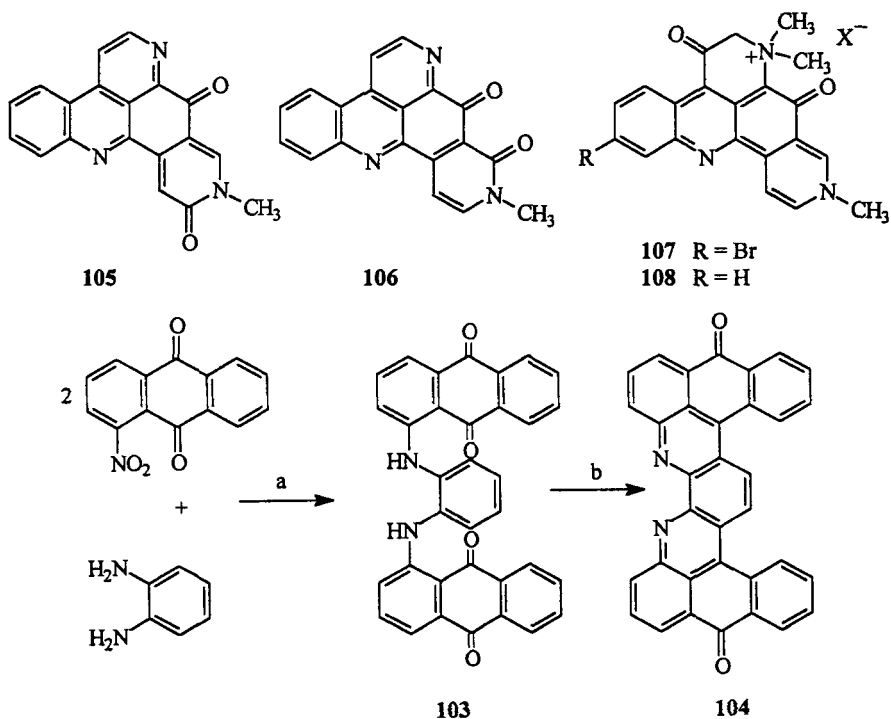
SCHEME 18



SCHEME 19. (a) H₂O, reflux, 22%; (b) paraffin oil, N₂, 320°C, 93%.

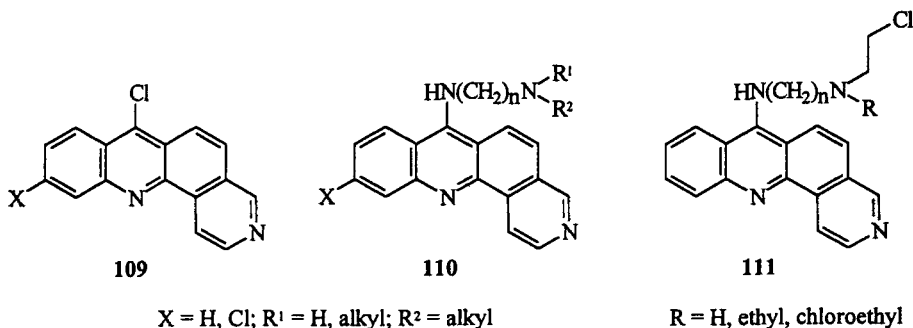
3. Pyrido[3,4-*c*]acridines (Benzo[*b*][1,8]phenanthrolines)

The pentacyclic pyridoacridine alkaloids (amphimedine **105**, neoamphimedine **106**, petrosamine **107**, and debromopetrosamine **108**) also contain this ring skeleton (see pyrido[2,3-4-*kl*]acridines).

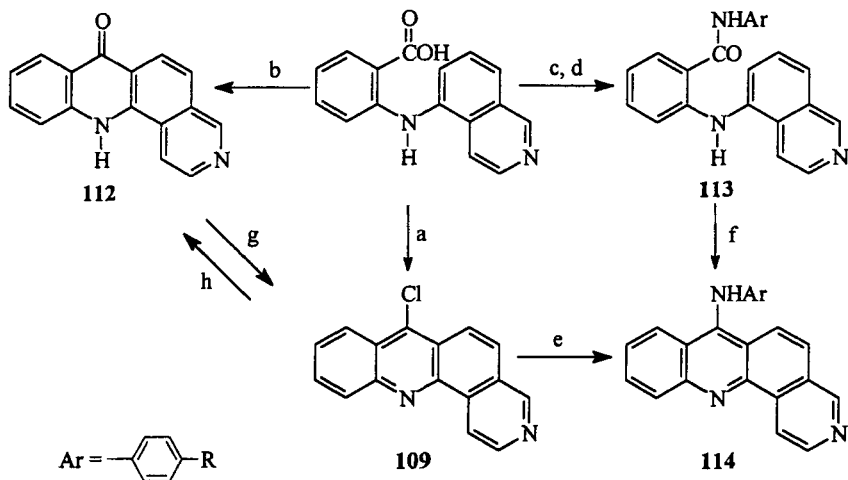


SCHEME 20. (a) Na₂CO₃, Cu-bronze, PhNO₂; (b) 70% H₂SO₄, 160°C, 73% (a,b).

Elslager and Tendick (62JMC546) prepared 7-chloro[*b*][1,8]phenanthrolines **109**, via Ullmann-amine coupling followed by cyclization, a route described in Scheme 1, but with 5-aminoisoquinoline, and converted them to potential amebicidal 7-(mono- and dialkylaminoalkylamino)benzo[*b*][1,8]phenanthrolines **110**.



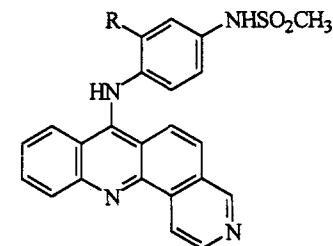
7-Chlorobenzo[*b*][1,8]phenanthroline **109** ($X = \text{H}$) was later used by Creech *et al.* (72JMC739) to prepare nitrogen mustard derivatives **111** of benzo[*b*][1,8]phenanthroline as antitumor agents, and by Sánchez *et al.* (90H2003) to prepare a series of 7-anilino derivatives of benzo[*b*][1,8]phenanthroline **114**. These anilino derivatives **114** were also prepared to cyclization of 2-(isoquinoline-5'-yl)benzanilides **113** with POCl_3 (Scheme 21)



SCHEME 21. $R = \text{F, OMe, NMe}_2, \text{NHCOMe, SO}_2\text{Me, SO}_2\text{NH}_2, \text{NHSO}_2\text{Ph, NHSO}_2\text{-}p\text{-C}_6\text{H}_4\text{Me}$. (a) POCl_3 , reflux, 39%; (b) H_2SO_4 , heat, 60%; (c) PCl_5 ; (d) ArNH_2 , EtOH, MeSO_3H ; (e) ArNH , C_6H_6 , moderate; (f) POCl_3 , reflux, 42–62%, (c,d,f); (g) POCl_3 , PCl_5 ; (h) H_3O^+ .

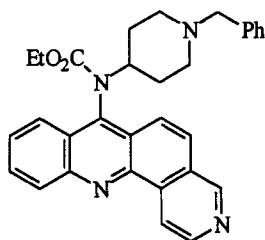
(90H2003). Biological evaluation of these anilino derivatives **114** along with 7-chlorobenzo[*b*][1,8]phenanthroline **109** ($X = H$) and benzo[*b*][1,8]-phenanthroline-7(12*H*)-one **112** showed a tight binding tendency with DNA. Significant inhibition of L1210 murine leukemia cells by benzo[*b*]-[1,8]phenanthroline-7(12*H*)-one **112** demonstrated that the anilino side chain was unnecessary for activity. No change in the activity was observed on substitution of electron-withdrawing or electron-donating substituents onto the aniline ring. 7-Chlorobenzo[*b*][1,8]phenanthroline **109** was found to be inactive (93JPS262).

Denny and Baguley (87MI1) used diphenyl iodonium-2-carboxylate **55** as an *N*-aryllating agent in an Ullmann-amine coupling step, as described in Scheme 9, but with 5-aminoisoquinoline, and prepared some 7-anilino-benzo[*b*][1,8]phenanthrolines **115**. None of the anilino derivatives showed significant activity against the P388 leukemia and Lewis lung solid tumor, although they displayed tight binding with DNA. Another derivative **116** of benzo[*b*][1,8]phenanthroline was tested as an antinociceptive agent but was found to be inactive (91MI1).



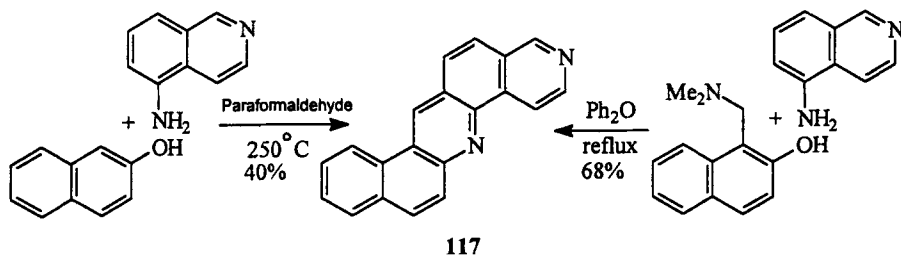
R = MeO, MeNH, Me₂N

115



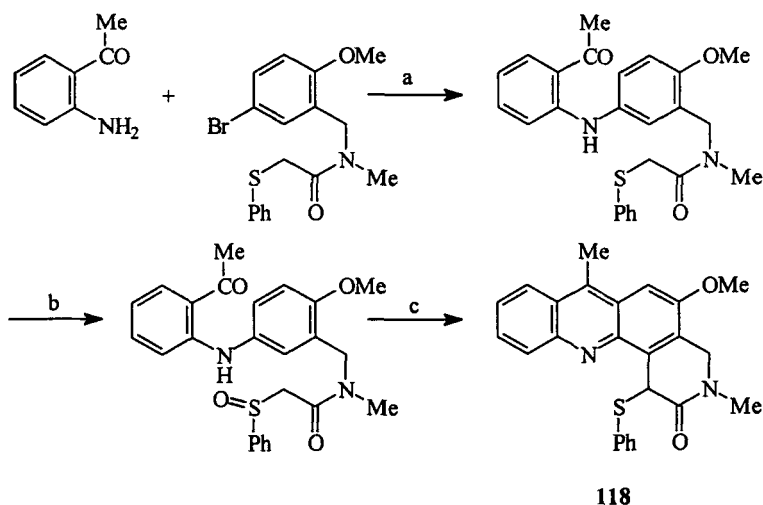
116

The Ullmann-Fetvadjan reaction has been applied to 5-aminoisoquinoline to prepare naphtho[2,1-*b*][1,8]phenanthrolines, such as **117** (Scheme 22) [67JCS(C)213; 80JCS(P1)1233].



117

SCHEME 22

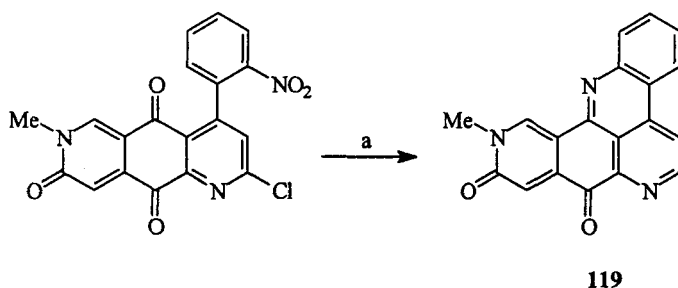


SCHEME 23. (a) Na_2CO_3 , Cu, PhNO_2 , reflux, 59%; (b) MCPBA, CH_2Cl_2 , 0°C to rt, 87%; (c) H_2SO_4 , AcOH, 130°C , 37%.

In the development of pyridone fused acridines, Kennedy *et al.* used a sulfoxide-based route to produce 3,7-dimethyl-5-methoxy-1-phenylthio-1,2,3,4-tetrahydro-2-oxobenzo[*b*][1,8]phenanthroline **118** (Scheme 23) [91-JCS(P1)2499].

4. Pyrido[4,3-*c*]acridines (Benzo[*b*][1,9]phenanthrolines)

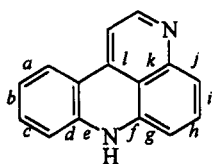
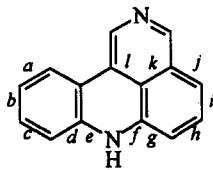
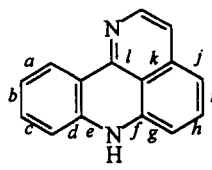
Kubo and Nakahara have reported the formation of an isomer **119** of amphimedine **105**, which possesses this novel ring system (Scheme 24) (88H2095).



SCHEME 24. (a) 10% Pd/C, Et_3N , MeOH, rt 20 h, 18%.

D. PYRIDO[*kl*]ACRIDINES

In this class, the extra pyridine ring is fused at bonds *k* and *l* of the acridine. Three types of pyrido[*kl*]acridines **120** are possible, depending on the position of the nitrogen in the fused pyridine ring.

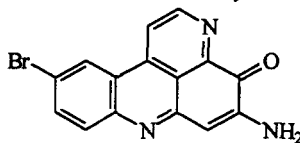
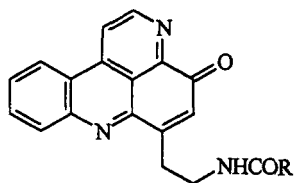
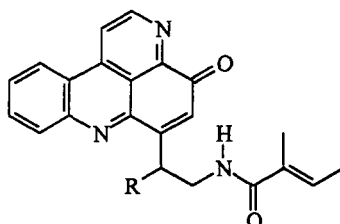
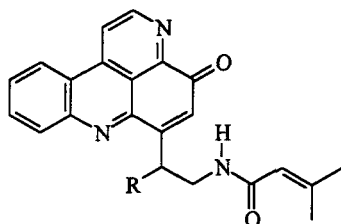
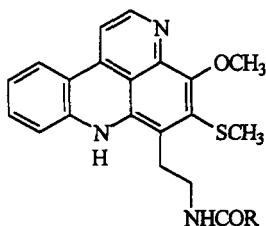
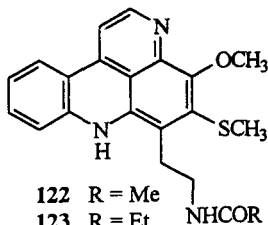
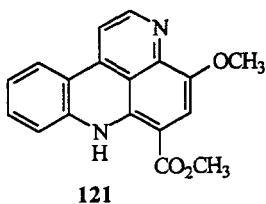
**120a****120b****120c**1. *Pyrido*[2,3,4-*kl*]*acridines*

a. *Isolation and Biological Activity.* The polycyclic aromatic alkaloids based on the pyrido[2,3,4-*kl*]acridine skeleton are members of a fast-growing class of marine sponge and ascidian (tunicate) metabolites. More than 50 alkaloids of this class have been isolated and characterized during the past 12 years.

Norsegoline **121** is the simplest member of this class isolated from *Eudistoma* sp., a tunicate (88TL3861; 89JOC5331). Other tetracyclic alkaloids include varamines A **122** and B **123**, lissoclines A **124** and B **125**, diplamine **126**, cystodytins A–J **128–137**, and pantherinine **138**. Varamines A **122** and B **123**, isolated from the ascidian *Lissoclinum vareau*, are brilliant red pigments that were found to be cytotoxic toward L1210 murine leukemia, with IC_{50} values of 0.03 and 0.05 $\mu\text{g/ml}$, respectively (89JOC4256). Lissoclines A **124** and B **125**, isolated from *Lissoclinum* sp. collected from the Great Barrier Reef, Australia, did not show significant activity against the fungus *Candida albicans* (94JOC6600). Diplamine **126**, another tetracyclic alkaloid isolated from the tunicate *Diplosoma* sp., showed cytotoxicity towards L1210 murine leukemia cells ($IC_{50} = 0.02 \mu\text{g/ml}$) (89TL4201) and human colon cancer cell lines ($IC_{50} < 1.4 \mu\text{M}$) (94JMC3819). DNA intercalation and topoisomerase II inhibition ($IC_{90} = 9.2 \mu\text{M}$) by diplamine **126** was also observed (94JMC3819). The isolation of another homolog of this series, “isobutyramide” **127**, from an unidentified tunicate has been reported (93CRV1825).

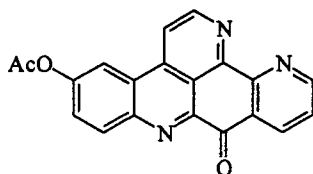
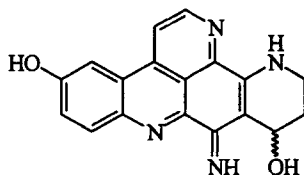
The tunicate *Cystodytes dellechiaiei* is a very rich source of pyrido[2,3,4-*kl*]acridine alkaloids. Nine tetracyclic alkaloids, cystodytins A–I **128–136**, have been isolated from this species (88JOC1800; 91JNP1634). Except for cystodytin C **130**, all other cystodytins were isolated as inseparable isomeric pairs (3.5:1) of cystodytins, β,β -dimethylacrylate and tiglate amides

[cystodytins A **128** and B **129**, D **131** and E **132**, F **133** and G **134**, and H **135** and I **136**]. Cystodytin J **137**, isolated from a Fijian *Cystodytes* sp., was found to be a good DNA intercalator, a potent inhibitor of topoisomerase II ($IC_{90} = 8.0 \mu M$), and a potent cytotoxin against the human colon tumor cell line HCT 116 ($IC_{50} = 1.6 \mu M$) (94JMC3819). Cystodytins A–C **128–130** showed powerful Ca^{2+} releasing activity in sarcoplasmic reticulum and cytotoxicity against L1210 murine leukemia cells ($IC_{50} \sim 0.2 \mu g/ml$) (88JOC1800). Cytotoxic activity ($IC_{50}s = 0.68\text{--}1.4 \mu g/ml$) against both



L1210 cells and epidermoid carcinoma KB cells was also observed for other cystodytins (91JNP1634). A bromo-substituted tetracyclic alkaloid pantherinine **138** has been isolated from the ascidian *Aplidium pantherinum*, and a moderate cytotoxic activity ($ED_{50} = 4.5 \mu\text{g/ml}$) against P388 murine leukemia cells has been reported by Kim *et al.* (93JNP1813).

Pentacyclic alkaloids contain an additional fused heterocyclic ring, such as tetrahydropyridine, pyridine (pyridone), thiazine, or thiazole. Calliactine was shown to be a pyridoacridine alkaloid (87T4023) nearly half a century after its isolation from the Mediterranean anemone *Calliactis parasitica* in 1940 (40BSF608). Although the exact structure of the alkaloid is still unclear, the structural analysis shows that it contains an additional tetrahydropyridine ring (87T4023). The structure of neocalliactine acetate **139**, derived from calliactine by heating with water (aromatization) followed by reaction with acetic anhydride, has been established by a total synthesis (92LA1205; 93H943). On the basis of spectral data and the establishment of the neocalliactine acetate **139** structure, structure **32** is the most favorable among the four proposed by Cimino *et al.* for calliactine (87T4023).

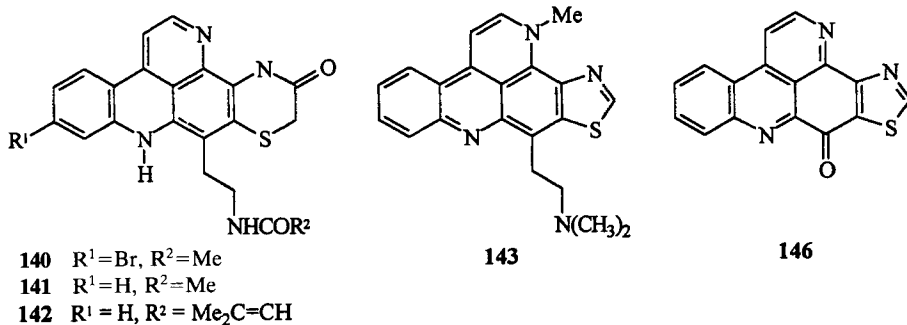
**139****32**

Amphimedine **105**, the first pyridoacridine to be fully characterized, was isolated from the Guamanian sponge, *Amphimedon* sp. (83JA4835). Its regioisomer, neoamphimedine **106**, was isolated from the Micronesian sponge *Xestospongia* cf. *carbonaria*, along with amphimedine **105** and debromopetrosamine **108** (93CRV1825). Neoamphimedine **106** was found to be a potent inhibitor of mammalian topoisomerase II ($IC_{50} = 1.3 \mu\text{M}$), but not of topoisomerase I. Intercalation of neoamphimedine **106** into DNA was observed with a K_m of $2.8 \times 10^5 \text{ M}^{-1}$ and a binding site size of 1.8 base pairs per molecule. Amphimedine **105**, debromopetrosamine **108**, and petrosamine **107** (from the sponge (*Petrosia* sp.) have little effect on topoisomerase I or II activity, despite comparable cytotoxicity (40BSF608).

Ascididemin **28**, from *Didenum* sp. (88TL1177), and 2-bromoleptoclinidone **29**, from *Leptoclinides* sp. (87JA6134; 89TL1069), were the first polycyclic aromatic metabolites to be isolated from ascidians. Both compounds show cytotoxicity toward leukemia cell lines with IC_{50} s of $0.4 \mu\text{g/ml}$, whereas ascididemin also inhibits topoisomerase II ($IC_{50} = 75 \mu\text{M}$) and causes release of calcium ions in the sarcoplasmic reticulum (91JOC804). Two

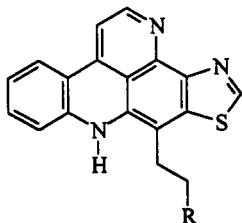
regioisomers, meridine **50** and 11-hydroxyascididemin **30** were isolated from the ascidians *Amphicarpa meridina* and *Leptoclinides* sp., respectively (91JOC804). Both of these isomers, along with 8,9-dihydro-11-hydroxyascididemin **31**, have also been isolated from the Okinawan marine sponge *Biemna* sp. (93T8337). Meridine **50** exhibits cytotoxicity against P388 murine leukemia cells ($IC_{50} = 0.3\text{--}0.4\text{ }\mu\text{g/ml}$) (91JOC804), and 8,9-dihydro-11-hydroxyascididemin **31** exhibits cytotoxicity against human epidermoid carcinoma KB ($IC_{50} = 0.2\text{ }\mu\text{g/ml}$) and murine lymphoma L1210 ($IC_{50} = 0.7\text{ }\mu\text{g/ml}$) cells *in vitro* (93T8337). A new pentacyclic alkaloid, cystodamine **51**, has been isolated from the ascidian *Cystodytes dellechiaiei* (94TL7023). The new alkaloid shows cytotoxicity against CEM human leukemic lymphoblasts ($IC_{50} = 1.0\text{ }\mu\text{g/ml}$).

Shermilamines A **140**, B **141**, and C **142** are thiazinone-containing pentacyclic alkaloids isolated from the purple tunicate *Trididemum* sp. (**140** and **141**) (88JOC4619; 89JOC4231) and a Fijian *Cystodytes* sp. (**141** and **142**) (94JMC3819). Shermilamine B **141** has been reported to exhibit cytotoxicity against KB cells ($IC_{50} = 5.0\text{ }\mu\text{g/ml}$) (91JOC804) and HCT cells ($IC_{50} = 13.8\text{ }\mu\text{M}$) (94JMC3819), and shermilamine C **142** exhibits cytotoxicity against HCT cells ($IC_{50} = 16.3\text{ }\mu\text{M}$). Shermaline B **141** and C **142** also inhibit topoisomerase II ($IC_{90} = 118\text{ }\mu\text{M}$ and $138\text{ }\mu\text{M}$, respectively) (94JMC3819).



A series of pentacyclic aromatic alkaloids that incorporate a thiazole ring were isolated from sponges, ascidians (tunicates), and the lamellariidae mollusk *Chelynotus semperi*. Dercitin **143** (88JA4356; 92JOC1523), a metabolite of deep-water sponge *Dercitus* sp., exhibits a remarkable biological activity. It inhibits a variety of cultured cell clones at nanomolar concentrations and exhibits antitumor activity (in mice) and antiviral activity (against herpes simplex and A-59 murine corona virus) at micromolar concentrations. Burres *et al.* (89MI2) observed the inhibition of both DNA and RNA syntheses by dercitin **143** by up to 83% at 400 nM and inhibition of protein synthesis to a lesser extent. Inhibition of DNA polymerase and DNase nick translation at 1.0 nM by dercitin **143** was also reported. Dercitin showed a

potent intercalation into nucleic acids and little inhibition of topoisomerases (89MI2). New structural types of anti-HIV drugs based on dercitin have been proposed by Taraporewala *et al.* (92JMC2744).

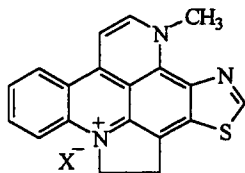


- 144** R = Me₂N
145 R = MeNH
147 R = Me₂CHCH₂CONH
148 R = EtCONH
149 R = MeCONH
150 R = Me₂C=CHCONH

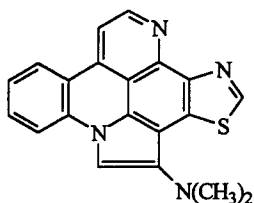
Nordercitin **144**, dercitamine **145**, and dercitamide (kuanoniamine C) **148** were also isolated from *Dercitus* sp. and *Stelletta* sp., along with dercitin **143** (89TL4359; 92JOC1523). Kuanoniamines A–D **146–149** and shermilamine B **141** were found in the mollusc *Chelynotus semperi* and its prey, an unidentified tunicate (90JOC4426). A new kuanoniamine, the dehydrokuanoniamine B **150**, has been isolated along with kuanoniamine D **149** and other alkaloids from a Fijian *Cystodytes* sp. (94JMC3819). Kuanoniamines A **146**, B **147**, and D **149** exhibit cytotoxicities against KB cells, with IC₅₀ values of 2.0, >10, and 1.0 μg/ml, respectively (90JOC4426). Cytotoxicities against HCT cells (IC₅₀ 7.8 and 8.3 μM) for dehydrokuanoniamine B **150** and kuanoniamine D **149** were also reported (94JMC3819). Kuanoniamine D **149** can form complexes with Fe(II), Co(II), Cu(II), and Zn(II) ions (92JOC1523).

Two hexacyclic alkaloids, cyclodercitin **151** and stelletamine **152** from *Stelletta* sp. (89TL4359; 92JOC1523), and three optically active hexacyclic alkaloids, segoline A **153**, segoline B **154**, and isosegoline A **155** from the Red Sea tunicate, *Eudistoma* sp., have been isolated along with tetra- and pentacyclic alkaloids (88TL3861; 89JOC5331). Another interesting compound isolated from *Eudistoma* sp. was the symmetrical, heptacyclic eilatin **33** (88TL6655; 94JMC3819). Cytotoxicity (IC₅₀ = 5.3 μM) of eilatin **33** against HCT cell lines has been reported (94JMC3819). This compound was also found to regulate cell growth and to affect cAMP-mediated cellular processes (93MI1). Because of the presence of the 1,10-phenanthroline skeleton, eilatin **33** is capable of chelating metal ions such as Ni(II) (88TL6655).

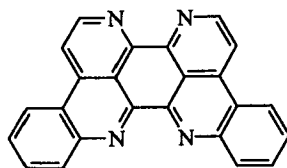
Two octacyclic alkaloids, eudistones A **48** and B **49**, along with ascidide-min **28**, have been isolated from another tunicate of the genus *Eudistoma* (from the Seychelles) (91JOC5369). These compounds are optically active, but their absolute configurations are still unknown. Another octacyclic alkaloid, biemnadin **34**, isolated from the Okinawan marine sponge *Biemna*



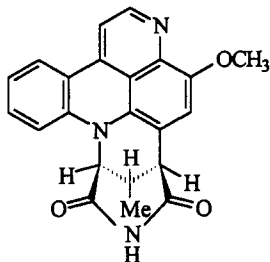
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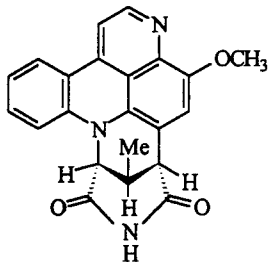
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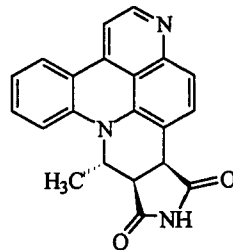
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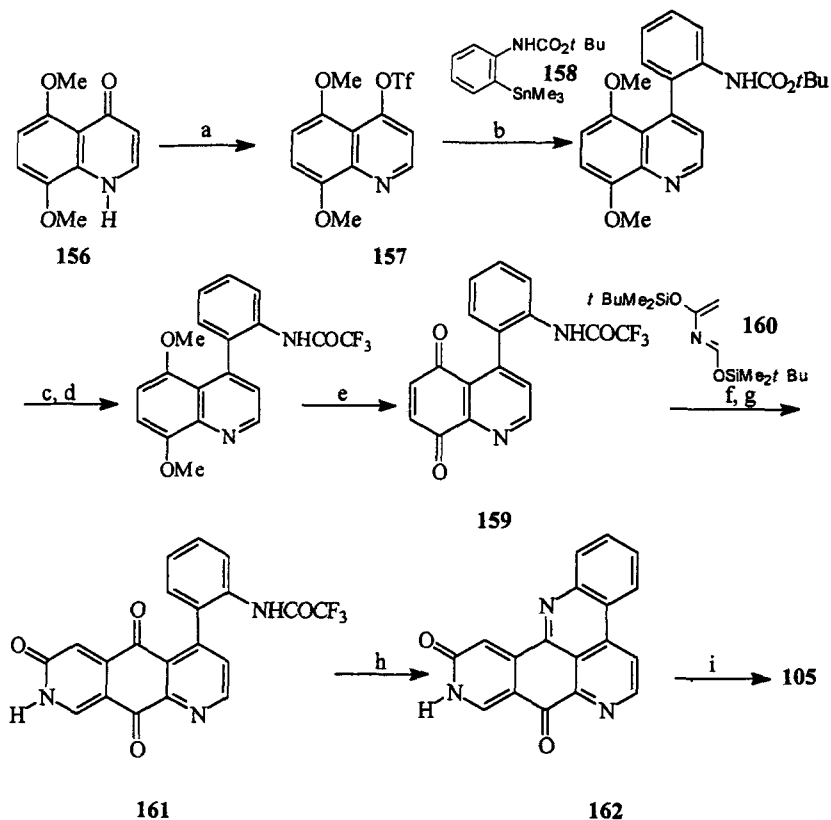
155

sp., has been shown to exhibit cytotoxicity against human epidermoid carcinoma KB and murine lymphoma L 1210 cells *in vitro* (93T8337).

b. *Syntheses.* The biological activity and the novel ring systems of these pyridoacridine alkaloids make them appealing targets for synthesis. A number of approaches have been developed for the synthesis of these compounds.

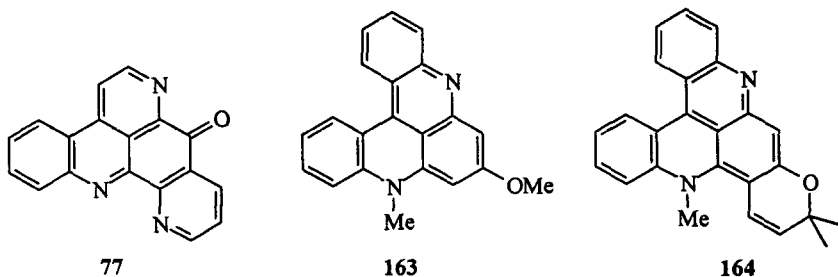
Imine formation. An example of this route is Echavarren and Stille's use of a simple intramolecular imine formation between a quinone moiety and an amino group to complete the nucleus (Scheme 25) of amphimedine **105** (88JA4051). The quinone **159** was prepared by a palladium-catalyzed cross-coupling of 5,8-dimethoxyquinolin-4-yl triflate **157** (from 5,8-dimethoxyquinolin-4-one **156**) with 2-*t*-butoxycarbonyl-aminophenyl-trimethyltin **158**, followed by deprotection of the amino group, reprotection by the trifluoroacetyl group, and then oxidation with ceric ammonium nitrate (CAN). The aza-Diels–Alder reaction of the resultant quinone **159** with Ghosez's diene **160** afforded an intermediate **161**. Deprotection of the amino group with aq. HCl and *in situ* formation of the imine gave a precursor **162** of the amphimedine **105**, which was obtained by methylation with dimethyl sulfate.

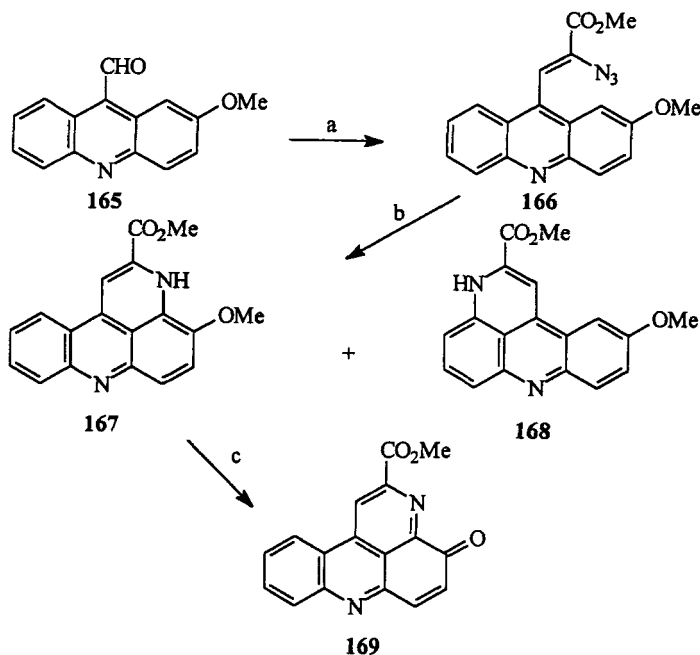
Similar strategies have been employed by Kubo and Nakahara (88H2095) for the synthesis of amphimedine **105**; by Szczepankiewicz and Heathcock (94JOC3512) for the synthesis of diplamine **126**; by Nakahara *et al.* (93H1139) for the synthesis of eilatin **33**; by Gómez-Bengoia and Echavarren



SCHEME 25. (a) $(\text{Tf})_2\text{O}$, 2,6-lutidine, CH_2Cl_2 , 92–95%; (b) $\text{Pd}(\text{PPh}_3)_4$, LiCl , dioxane, 7 h, 100°C ; (c) TFA; (d) TFAA, $(i\text{Pr})_2\text{NEt}$, 82–87% (b,c,d); (e) CAN, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 23°C , 15 min; (f) THF, 23°C , 16 h; (g) pyridinium–HF, 48% (e,f,g); (h) 6 M HCl, THF aq., $70\text{--}80^\circ\text{C}$, 86%; (i) Me_2SO_4 , K_2CO_3 , DME, 96%.

(91JOC3497) for the synthesis of isoascididemin **77**, a regioisomer of the naturally occurring ascididemin **28**; and by Jolivet *et al.* for the synthesis of a series of quino- and pyranoquinoacridines, such as **163** and **164** [95JCS(P1)2333].



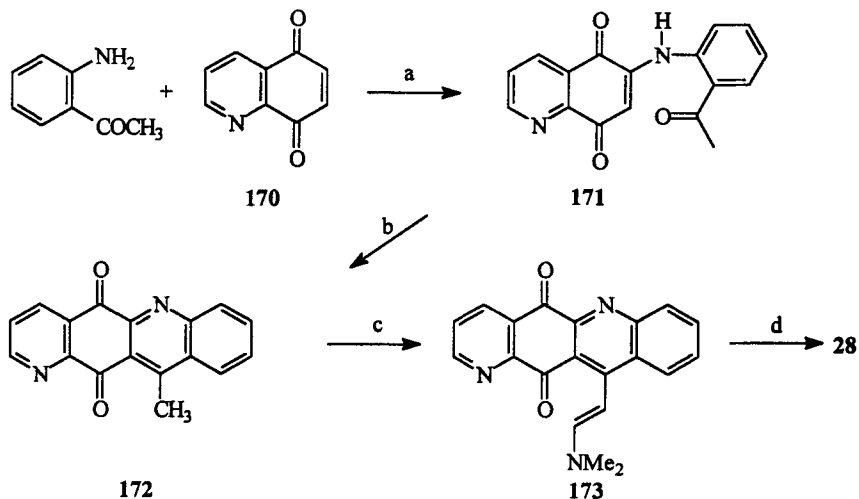


SCHEME 26. (a) $\text{MeO}_2\text{CCH}_2\text{N}_3$, NaOMe, MeOH, -10 to 0°C , 48%; (b) xylene, 140°C , 78% (**167**), 19% (**168**); (c) $\text{MnO}_2/\text{H}_2\text{SO}_4$, 75%.

Nitrene insertion. A nitrene insertion reaction is central to many syntheses of pyridoacridine alkaloids and their analogues. For example, Labarca *et al.* [87JCS(P1)927] have reported a three-step synthesis of a pyridoacridine **169** starting from 2-methoxyacridine-9-carboxaldehyde **165** (Scheme 26). Cyclization of the vinyl azide **166** by thermolysis is believed to involve a nitrene insertion reaction, to give either **167** or **168**.

Ciufolini and his co-workers have completed the total syntheses of pyridoacridine alkaloids such as cystodytins A **128** (91JA8016), B **129** (91JA8016), and J **137** (92JA10081), diplamine **126** (92JA10081), dercitin **143** (92JA10081; 95JA12460), nordercitin **144** (92JA10081; 95JA12460), kuanoniamine D **149** (92JA10081; 95JA12460), and shermilamine B **141** (92JA10081) by using nitrene insertion methodology. Nitrene insertion is also involved in the Gellerman synthesis of the pyrido[2,3,4-*k*]acridines (92TL5577), and a similar approach was used by McKillop and his co-workers for the synthesis of norsegolone **121** and other analogs [92-JCS(CC)1453; 93JCS(P1)879].

Cyclodehydration. This route has been used by Bracher for the synthesis of ascididemin **28** (Scheme 27) (89H2093). Freshly prepared 2-aminoaceto-



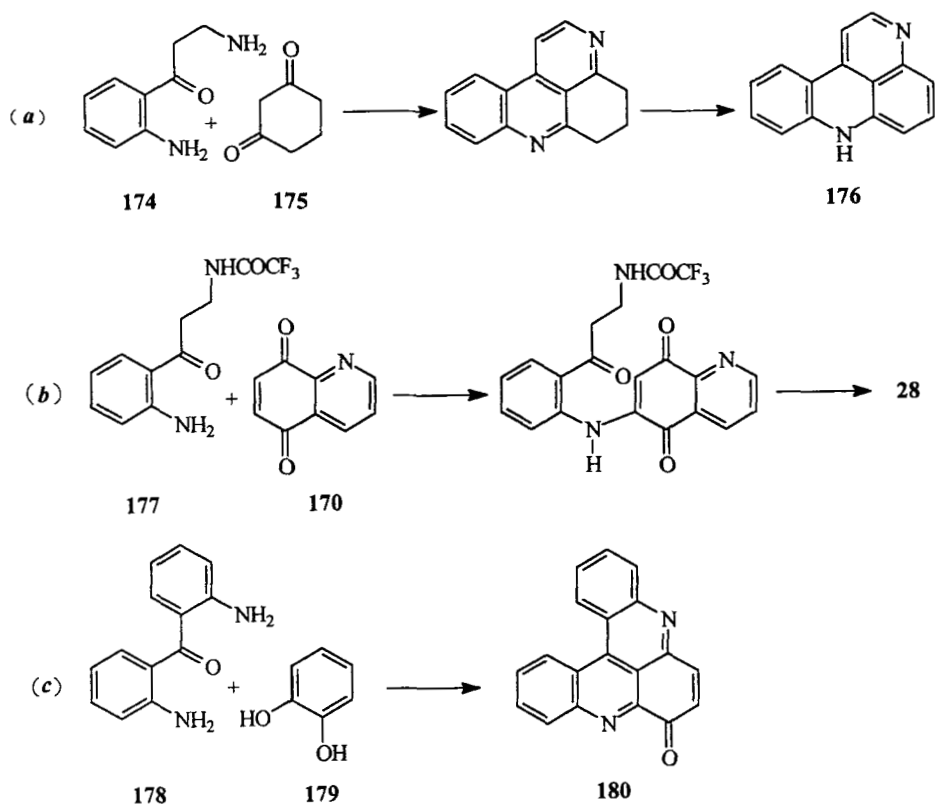
SCHEME 27. (a) O_2 , $Ce(SO_4)_2$, 78%; (b) $AcOH/H_2SO_4$, 94%; (c) $Me_2NCH(OEt)_2$, DMF; (d) NH_4Cl , $AcOH$, 59% (c,d).

phenone was used for oxidative amination of *p*-quinolinoquinone **170** in the presence of air and cerium ions, to give intermediate **171**, which cyclized to the linear pyridoacridine **172** on heating in a mixture of conc. sulfuric and acetic acids. Condensation of the side-chain methyl group of **172** with dimethylformamide diethyl acetal afforded an enamine **173**, which cyclized to ascididemin **28**.

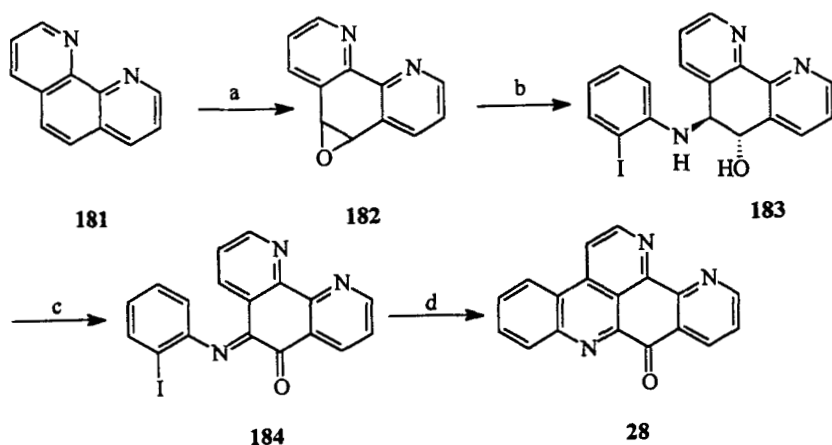
The same strategy has been applied to the preparation of a number of pyridoacridine alkaloids, which include 2-bromoleptoclidinone **29** (90LA205), 11-hydroxyascididemin **30** (93H943) and kuanoniamine A **146** (93H943), and also for the synthesis of neocalliactine acetate **139** (92LA1205; 93H943) (a derivative of calliactine **32**).

Biomimetic synthesis. Kashman and his co-workers have reported novel biomimetic syntheses of pyrido[2,3,4-*kl*]acridines by the reaction of kinuramine **174** or its derivatives, such as **177**, and other analogs, such as **178**, with a variety of diones (e.g., **175**), quinones (e.g., **170**), and hydroquinones (e.g., **179**) (Scheme 28) (93TL1823; 93TL1827; 94S239, 94T12959). Using this strategy they have prepared a number of pyridoacridines, including the marine alkaloids, eilatin **33** (93TL1827), ascididemin **28** (94S239), their derivatives, and other analogs such as **176** and **180** (93TL1823; 94T12959).

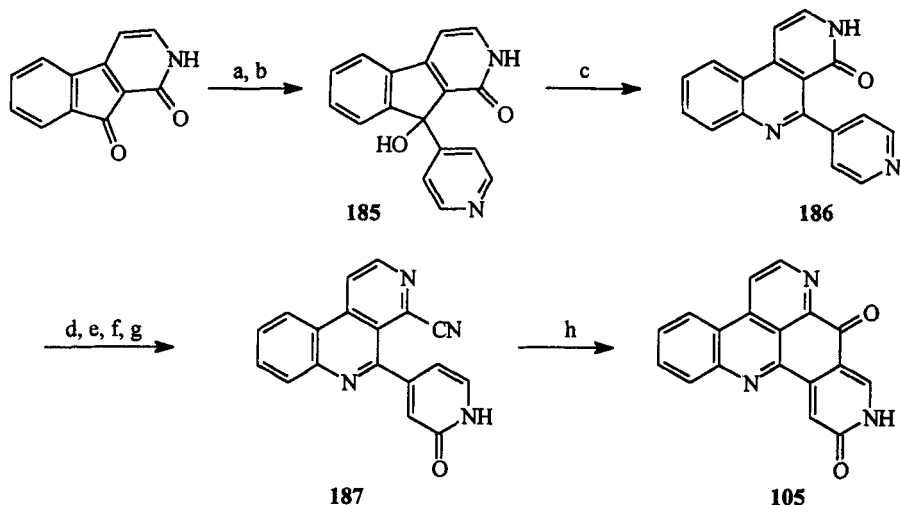
Miscellaneous syntheses. Moody *et al.* (90TL4375; 92T3589) have described a synthesis of ascididemin **28** that involves the epoxidation of 1,10-phenanthroline **181**, ring opening of the epoxide **182** with 2-iodoaniline to afford the amino alcohol **183**, and oxidation followed by photocyclization of the *o*-iminoquinone **184** (Scheme 29).



SCHEME 28



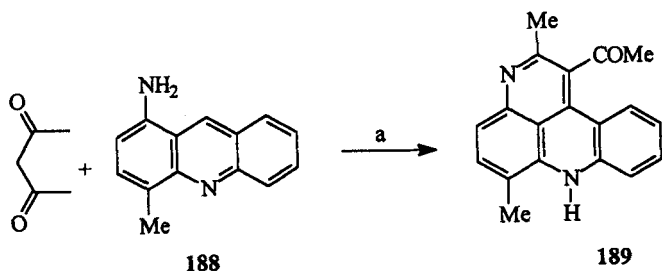
SCHEME 29. (a) NaClO, aq.; (b) 2-iodoaniline, Et₃Al, CH₂Cl₂, 79%; (c) Ba(MnO₄)₂, CH₂Cl₂, 83%; (d) *hν*, quartz, H₂SO₄, 32%.



SCHEME 30. (a) Me_3SiCl , Et_3N , THF, 60°C ; (b) 4-pyridylthium, -40 to 20°C , 2 h, 87% (a,b); (c) NaN_3 , PPA, 45°C , 20 h, 69%; (d) PCl_5 , DMF (cat.) POCl_3 , 180°C , 20 h; (e) MeOS_2OF , 20°C , 40 min; (f) KOH , $\text{K}_3[\text{Fe}(\text{CN})_6]$, 20°C , 10 h; (g) CuCN , DMSO, 150°C , 4 h, 38% (d,e,f,g); (h) PPA, 90°C , 5 h, 35%.

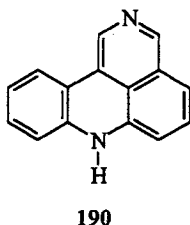
A novel synthesis of amphimedine **105** has been reported by Prager *et al.* (89H847; 91AJC277). It involves an azido ring expansion of a pyridylazafuorenol **185**, by the Schmidt reaction, to 5-(4-pyridyl)benzo[*a*]-[2,7]naphthyridin-4-one **186**, and then refunctionalization to the α -cyano precursor **187**, followed by cyclization in polyphosphoric acid (Scheme 30). Guillier *et al.* (95JOC292) have described a new synthesis of the intermediate **186**.

Taking advantage of the activity of the 9-position of acridines toward active methylenes, Gellerman *et al.* (92TL5577) have developed a



SCHEME 31. (a) AmOH , cat. H_2SO_4 , 130°C , 1.5 h.

method for the preparation of pyrido[2,3,4-*kl*]acridines starting from 1-aminoacridines. Thus, acid-catalyzed condensation of acetylacetone with 1-amino-4-methylacridine **188** gave a pyridoacridine **189** (Scheme 31).



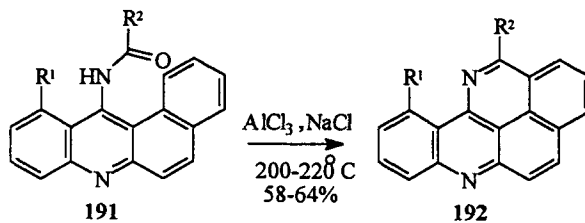
2. Pyrido[3,4,5-*kl*]acridines

No natural or synthetic compounds based on this ring system **190** have been reported.

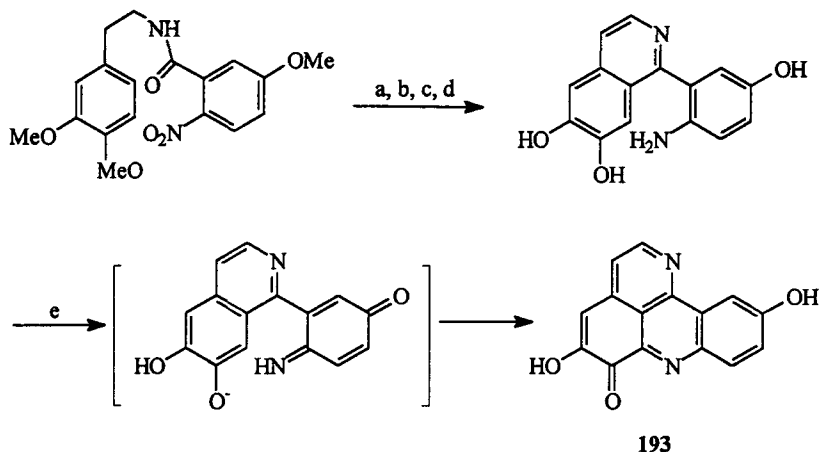
3. Pyrido[4,3,2-*kl*]acridines

Only a few examples of this ring system have been reported. Grout *et al.* [68JCS(C)2689] have cyclized *N*-acyl derivatives **191** of 9-aminobenzo[*a*]acridines to pyrido[4,3,2-*kl*]acridines **192** by heating with $\text{AlCl}_3/\text{NaCl}$ at 200–220°C (Scheme 32).

The only natural product based on this ring system is necatorone **193**. This alkaloid was isolated from a toadstool, *Lactarius necator* (84TL3575). This fungal metabolite showed a considerable mutagenic activity in the Ames test. A synthesis of necatorone **193** involving oxidative cyclization has been reported (Scheme 33) (85TL5975).



SCHEME 32. $\text{R}^1 = \text{H, Me}; \text{R}^2 = \text{H, Me}.$



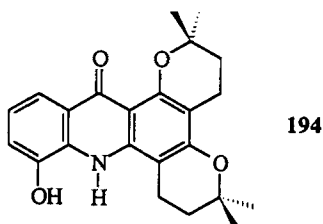
SCHEME 33. (a) POCl_3 , CH_3CN , 85–93%; (b) MnO_2 , C_6H_6 , reflux, 24 h, 90–98%; (c) 48% HBr , 64%; (d) $\text{H}_2/\text{Pd}-\text{C}$, 82–85%; (e) aq. NaOH (5%), O_2 , 67%.

III. Pyranoacridines

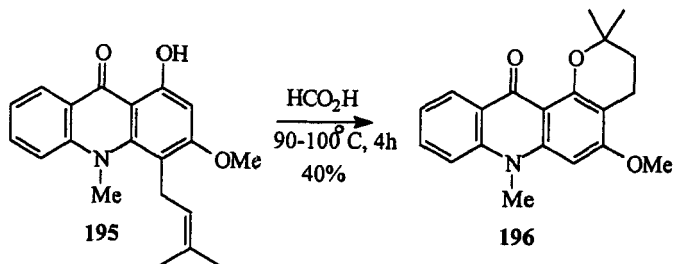
Only a few pyranoacridine ring systems have been reported in the literature.

A. PYRANO[2,3-*a*]ACRIDINES

The pentacyclic alkaloid bicyclo-*N*-methylatalaphylline **194**, isolated from *Atlantia monophylla* Correa, possesses this ring system as a part of its structure (72JOC3035). Formation of this ring system (e.g., **196**) from isoprene-containing acridone alkaloids or their derivatives (3-OH protected, e.g., **195**) has been reported (Scheme 34) [70T2905; 82P1771; 83JCS(P1)1681].



Bhavsar and his co-workers reported the formation of pyrano[2,3-*a*]acridin-2-ones, such as **199**, from 8-aryl-7-hydroxy-benzopyran-2-ones,

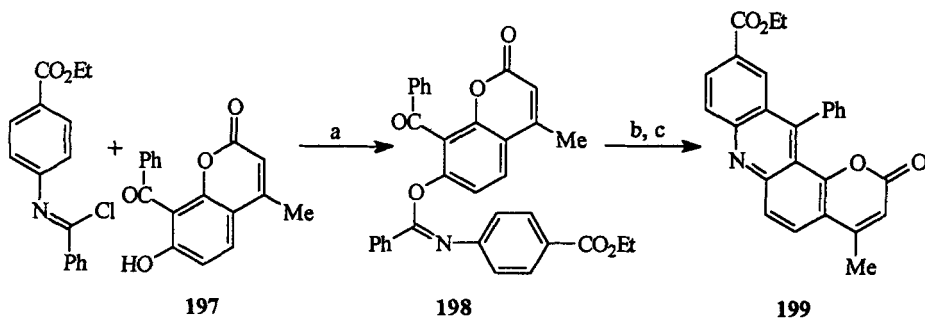


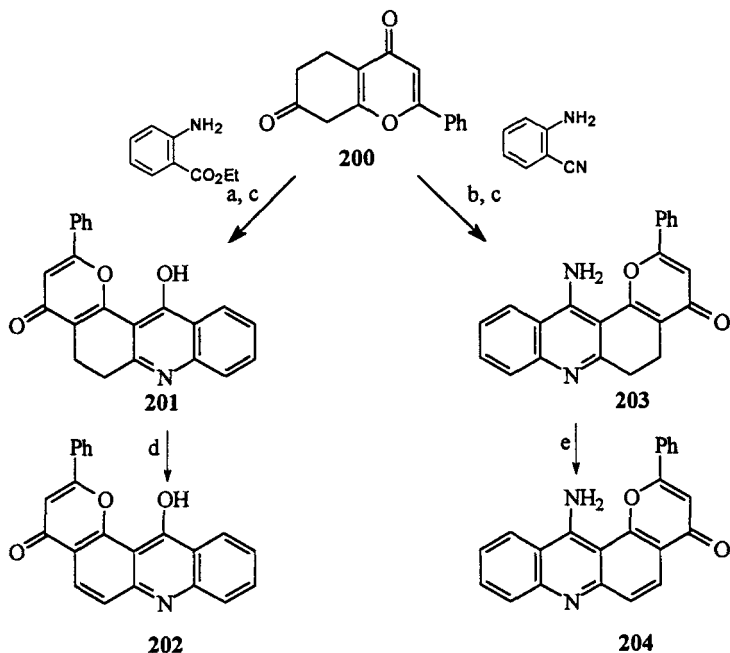
SCHEME 34

such as **197**, by using the Chapman–Mumm rearrangement of an imino ester **198** (Scheme 35) (87MI2, 87MI3).

We have described a novel method for the construction of this ring system that involves the condensation of 7-oxo-5,6,7,8-tetrahydroflavone **200** with ethyl anthranilate or anthranilonitrile, followed by base-catalyzed cyclization and then dehydrogenation of the dihydro derivatives, **201** and **203** (Scheme 36) [94JCS(P1)173]. 12-Amino-2-phenylpyrano[2,3-*a*]acridin-4-one APPA **204** was found to be a very potent inhibitor ($\text{IC}_{50} = 1.9 \mu\text{mol dm}^{-3}$) of the EGF-dependent proliferation of DHER cells, and of the spontaneous proliferation of a human gastric carcinoma cell line, MKN 45, with an IC_{50} of $0.1 \mu\text{mol dm}^{-3}$. In addition, APPA **204** was tested against 60 cancer cell lines as part of the NCI Developmental Therapeutics Program and was shown to have an activity profile similar to that of known topoisomerase II inhibitors.

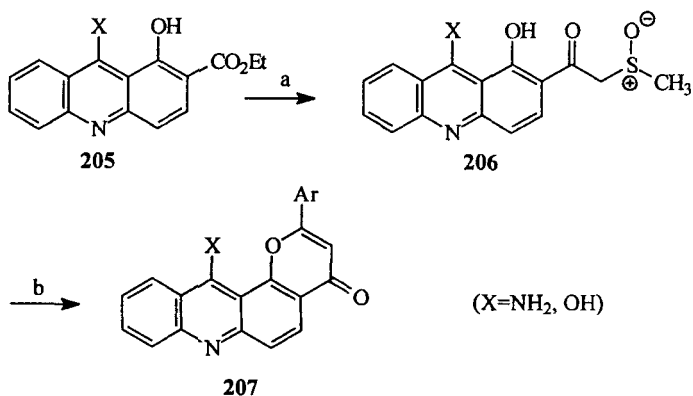
We have also developed an alternative synthesis [97JCS(P1) 601] of this ring system that utilizes the von Strandtmann flavone annellation procedure.

SCHEME 35. (a) Base, (b) heat, (c) H_3O^+ .



SCHEME 36. (a) PTSA, toluene, reflux, 47%; (b) PTSA, toluene, reflux, 65%; (c) NaNH₂, DME, reflux, 64% (**201**), 29% (**203**); (d) Hg(OAc)₂, DMSO, 51%; (e) MnO₂, toluene, reflux, 72%.

Thus, the esters **205** were treated with the dimsyl anion to give the β -ketosulfoxides **206**, which were cyclized to the pyranoacridinones **207** upon treatment with an aromatic aldehyde in the presence of piperidine (Scheme 37).

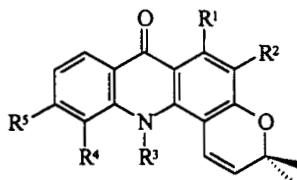
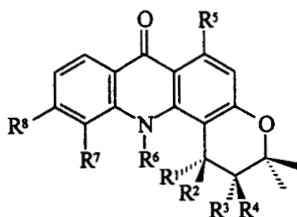
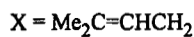


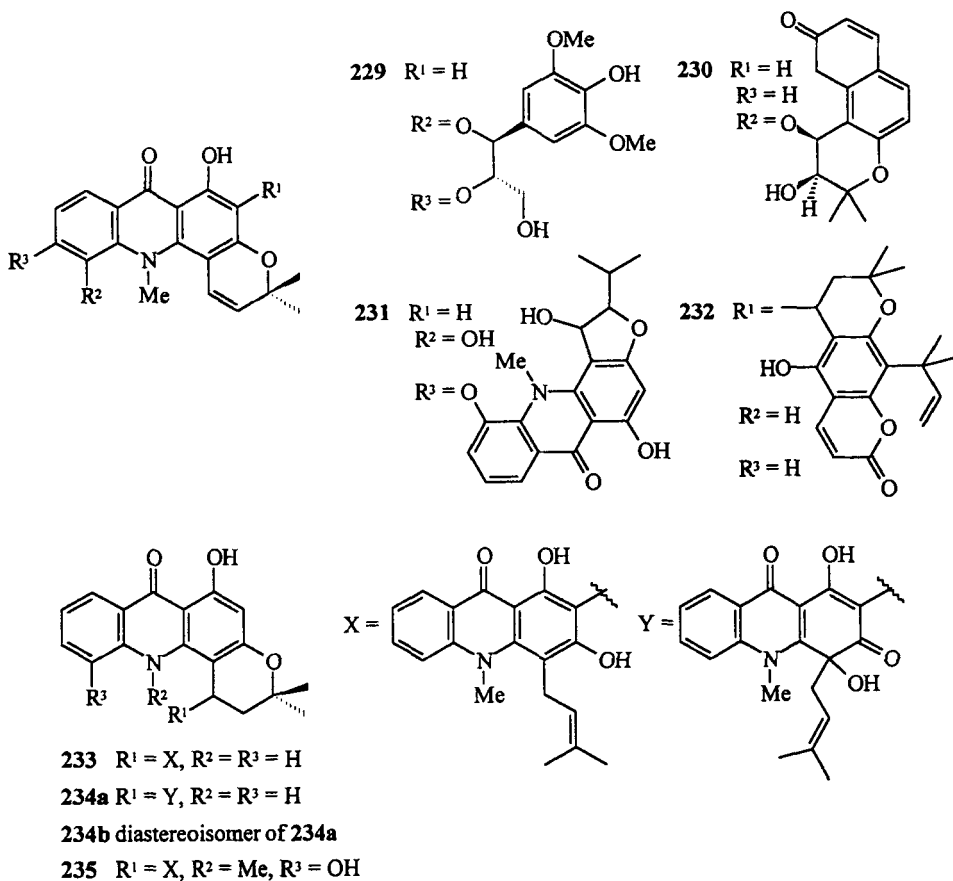
SCHEME 37. (a) ⁻CH₂SOCH₃, DMSO; (b) ArCHO, piperidine, DMSO.

B. PYRANO[2,3-*c*]ACRIDINES

1. Isolation and Biological Activity

Most of the pyranoacridone alkaloids are based on this ring system. Acronycine (acronine) **208** was the first pyranoacridine alkaloid to be isolated, in 1948 by Hughes and co-workers from the bark of *Baurella simplicifolia* (*Acronychia baueri*, an Australian Rutaceae plant) [48NAT(L)223] and in 1949 by Lahey and Thomas from *Vepris amphody* (49MI1). The correct structure was established in 1966 by degradative studies supported by NMR studies (66AJC275, 66T3245) and finally by X-ray crystallographic studies [70AX(B)853]. Acronycine **208** has broad-spectrum antineoplastic activity (85MI1; 89MI1; 92MI1), although its poor solubility in aqueous media is a major hindrance to its development as a clinical agent. Efforts were continued to isolate more alkaloids based on this skeleton, from other plants of Rutaceae family and also through molecular variation, to improve the cytostatic activity of acronycine **208**. Other alkaloids based on this system include noracronycine **209** [66T3245; 78MI1; 83JCS(P1)1681; 84JNP285], de-*N*-methylacronycine **210** [78MI1; 83JCS(P1)1681], de-*N*-methylnoracronycine **211** [78MI1; 83JCS(P1)1681], citracridone-I **212** [78MI1; 82H273; 83CPB901, 83JCS(P1)1681; 90JCS(P1)1593], citracridone-II **213** [82H273; 83CPB895; 90JCS(P1)1593], citracridone-III **214** (91H1781), 11-hydroxynoracronycine **215** [82H273; 83CPB895, 83JCS(P1)1681; 90JCS(P1)1593], 11-methoxynoracronycine (baiyamine A) **216** (86H1595), 11-hydroxy-20-methoxynoracronycine **217** (84JNP325), acrifoline **218** (95JNP1629), atalaphyllidine **219** (75E1387; 82IJC16), atalaphyllinine **220** [82IJC16, 82P1771; 83JCS(P1)1681], *N*-methylatalaphyllinine (11-hydroxy-*N*-methylseverifoline) **221** [82IJC16, 82P1771; 83JCS(P1)1681; 96P235], severifoline **222** (82P1771), *N*-methylseverifoline **223** [82P1771; 83JCS(P1)1681], acronycine epoxide **224** (88MI3), *trans*-1,2-dihydroxy-1,2-dihydrocitracridone-I **225** (95H187), (+)-1-hydroxy-1,2-dihydro-de-*N*-methylacronycine **226** (87H2057), (–)-*cis*-1,2-dihydroxy-1,2-dihydro-de-*N*-methylacronycine **227** (86JNP1091), 1-oxo-1,2-dihydro-de-*N*-methylacronycine **228** (87H2057), bicyclo-*N*-methylatalaphylline **194** (72JOC3035), acrignine **229** (93CPB406), neoacrimarines C **230** and D **232** (93CPB1757), ataline **231** [73JCS(CC)615], glycobisamines A–C **233**, **234a**, and **234b** [93JCS(P1)471], and buntanbismine **235** (96P221). These alkaloids have been isolated from various species of *Citrus*, *Glycosmis*, *Severinia*, *Sarcomelicope*, and other plants (all Rutaceae family), and some of them have demonstrated significant biological activity. For example, 11-hydroxynoracronycine **215** showed significant effects on Epstein–Barr virus-EA activation (95MI1), whereas glycobisamine A **233** showed *in vitro* antimalarial activity comparable to that of chloroquine diphosphate (91AAC377).

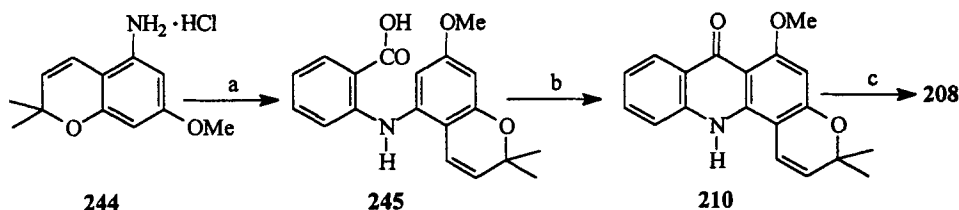
208 $R^1 = \text{OMe}, R^3 = \text{Me}, R^2 = R^4 = R^5 = \text{H}$ 209 $R^1 = \text{OH}, R^3 = \text{Me}, R^2 = R^4 = R^5 = \text{H}$ 210 $R^1 = \text{OMe}, R^2 = R^3 = R^4 = R^5 = \text{H}$ 211 $R^1 = \text{OH}, R^2 = R^3 = R^4 = R^5 = \text{H}$ 212 $R^1 = R^5 = \text{OH}, R^2 = \text{H}, R^3 = \text{Me}, R^4 = \text{OMe}$ 213 $R^1 = \text{OH}, R^2 = \text{H}, R^3 = \text{Me}, R^4 = R^5 = \text{OMe}$ 214 $R^1 = R^4 = R^5 = \text{OH}, R^2 = \text{H}, R^3 = \text{Me}$ 215 $R^1 = R^4 = \text{OH}, R^2 = R^5 = \text{H}, R^3 = \text{Me}$ 216 $R^1 = \text{OH}, R^2 = R^5 = \text{H}, R^3 = \text{Me}, R^4 = \text{OMe}$ 217 $R^1 = R^4 = \text{OH}, R^2 = \text{H}, R^3 = \text{Me}, R^5 = \text{OMe}$ 218 $R^1 = R^5 = \text{OH}, R^2 = R^3 = \text{H}, R^4 = \text{OMe}$ 219 $R^1 = R^4 = \text{OH}, R^2 = R^3 = R^5 = \text{H}$ 220 $R^1 = R^4 = \text{OH}, R^2 = \text{X}, R^3 = R^5 = \text{H}$ 221 $R^1 = R^4 = \text{OH}, R^2 = \text{X}, R^3 = \text{Me}, R^5 = \text{H}$ 222 $R^1 = \text{OH}, R^2 = \text{X}, R^3 = R^4 = R^5 = \text{H}$ 223 $R^1 = \text{OH}, R^2 = \text{X}, R^3 = \text{Me}, R^4 = R^5 = \text{H}$ 224 $R^1 = R^3 = R^7 = R^8 = \text{H}, R^5 = \text{OMe}, R^6 = \text{Me}, R^2R^4 = \text{O}$ 225 $R^1 = R^4 = R^5 = R^8 = \text{OH}, R^2 = R^3 = \text{H}, R^6 = \text{Me}, R^7 = \text{OMe}$ 226 $R^1 = R^3 = R^4 = R^6 = R^7 = R^8 = \text{H}, R^2 = \text{OH}, R^5 = \text{OMe}$ 227 $R^1 = R^3 = R^6 = R^7 = R^8 = \text{H}, R^2 = R^4 = \text{OH}, R^5 = \text{OMe}$ 228 $R^1R^2 = \text{O}, R^3 = R^4 = R^6 = R^7 = R^8 = \text{H}, R^5 = \text{OMe}$



2. Syntheses

Various approaches have been used to synthesize acronycine **208** and its derivatives. Lahey and Stick's synthesis (Scheme 38) involves the condensation of 2,3-dimethylchroman-5,7-diol **236** with anthranilic acid, followed by *N*-methylation of the minor product **238** to produce 1,2-dihydronoraacronycine **239** (73AJC2311).

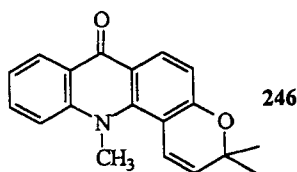
Beck *et al.* (68JA4706) have reported three interrelated syntheses of acronycine. One synthesis (Scheme 39) used 5,7-dimethoxy-1,2,3,4-tetrahydroquinolin-2(1*H*)-one **240**, which was coupled with 2-iodobenzoic acid to give the acid **241**. Ring closure with PPA, followed by refluxing with



SCHEME 40. (a) 2-Bromobenzoic Acid, $\text{Cu}(\text{AcO})_2$, KAcO , Et_3N , $t\text{BuOH}$, 58%; (b) TFAA, CH_2Cl_2 , rt, 3 days, 62%; (c) CH_3I , $\text{PhCH}_2\text{NEt}_3\text{Cl}$, NaOH (aq.), 2-butanone, 96%.

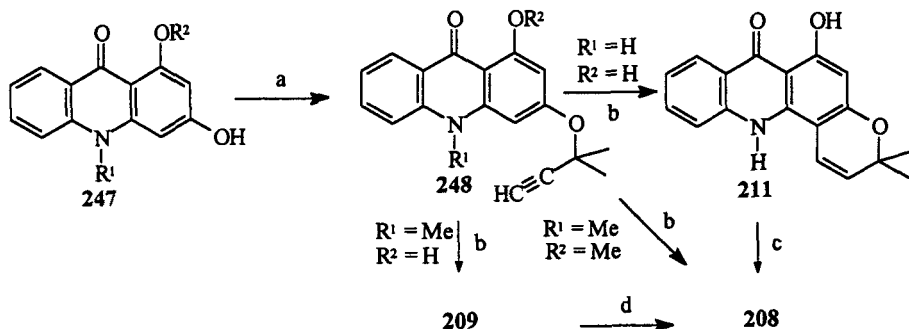
methanolic HCl , afforded methyl 1,3-dimethoxy-9-oxacridin-4-propionate **242**. Ether cleavage at C-1, followed by reaction with an excess of MeLi , yielded the tertiary alcohol **243**. Fusion with pyridinium chloride at high temperature caused O -demethylation at C-3 with concomitant ring closure. Treatment of the crude product with MeI under basic conditions produced dihydronoracronycine **239**. Dehydrogenation with DDQ afforded noracronycine **209**, which was converted to acronycine **208** by O -methylation with dimethyl sulfate.

Loughhead (90JOC2445) coupled 5-amino-2,2-dimethyl-7-methoxychromene **244** with 2-bromobenzoic acid, and the resultant product **245** was cyclized with TFAA. The de- N -methylacronycine **210** was then converted to acronycine **208** by methylation under phase-transfer conditions (Scheme 40). The same approach has been used by Elomri *et al.* to prepare 6-demethoxyacronycine **246** which was found to be more potent than acronycine **208** in some biological assays (92H799).



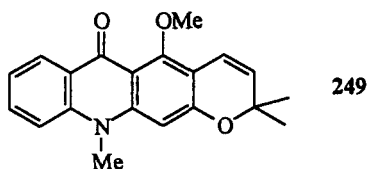
Hlubucek *et al.* annelated dimethylpyran rings onto 3-hydroxyacridones **247** by a Claisen-type rearrangement of their α,α -dimethyl propargyl ethers **248** (Scheme 41) [69CI(L)1809; 70AJC1881]. Similar strategies, with some modifications, were used by others to prepare acronycine **208** and its derivatives and analogs (72JMC266; 76JNP399; 82BSB33; 84LA31, 84T5181; 89AP31; 91AP67; 92JHC1293, 92M473; 93JHC1469).

Bandaranayaka *et al.* [74JCS(P1)998] devised an efficient synthesis of acronycine **208** that involves the condensation of 1,3-dihydroxyacridin-



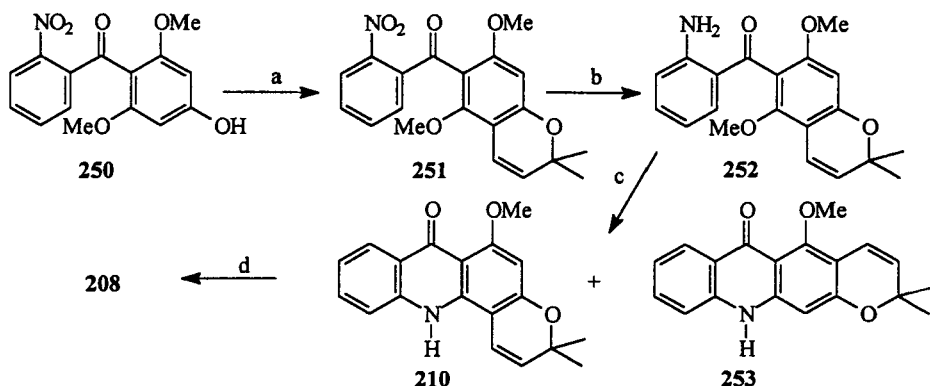
SCHEME 41. (a) $\text{HC}\equiv\text{C}-\text{C}(\text{CH}_3)_2\text{Cl}$, K_2CO_3 , KI, DMF, $50-70^\circ\text{C}$, N_2 , 14–18 h; (b) DMF, 130°C , 5h; (c) Me_2SO_4 , DMF, NaH, N_2 , 45°C , 1 h, 85%; (d) Me_2SO_4 , DMF, K_2CO_3 , N_2 , 60°C , 18 h, 86%.

9(10*H*)-one **247** ($\text{R}^1 = \text{R}^2 = \text{H}$) with 1,1-dimethoxy-3-hydroxy-3-methylbutane in pyridine at 150°C , followed by methylation of the angular pyranoacridine **211**, which was isolated by repeated crystallization. Methylation of the unpurified condensation product also gave isoacronycine **249** and noracronycine **209**, in addition to acronycine **208**. Use of citral and farnesal in place of 1,1-dimethoxy-3-hydroxy-3-methylbutane provided mono- or diprenyl-substituted acridones and their cyclized product. The same approach was used by Ramesh and Kapil [86IJC(B)684] to prepare 11-hydroxynoracronycine **215** and atalaphyllidine **219**.



Lewis and his co-workers have reported three interrelated syntheses of acronycine **208** (81T209). In one synthesis, 2,6-dimethoxy-4-hydroxy-2'-nitrobenzophenone **250**, obtained as a minor product from Friedel–Crafts acylation of 3,5-dimethoxyphenol with 2-nitrobenzoylchloride, was treated with 3-chloro-3-methylbut-1-yne under basic conditions. The resultant nitro compound **251** was reduced to the amine **252** with zinc. Upon reaction with sodium hydride in DMSO, this amine provided a mixture of de-*N*-methylisoacronycine **253** and de-*N*-methylacronycine **210**. De-*N*-methylacronycine **210** was converted to acronycine **208** by methylation with methyl iodide (Scheme 42).

Coppola (84JHC913) condensed *N*-methylisatoic anhydride **254** with the lithium enolate of 2,6,7,8-tetrahydro-2,2-dimethylbenzopyran-5-one **255** to

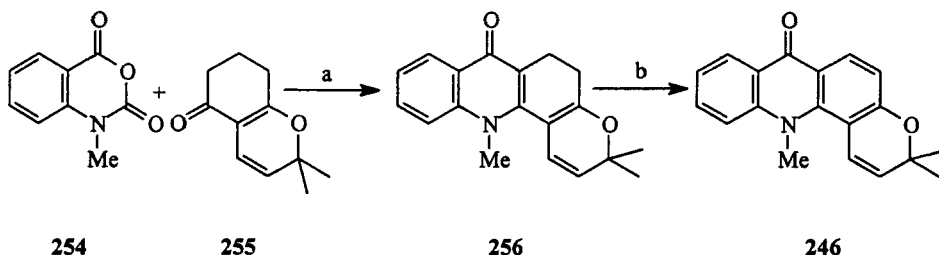


SCHEME 42. (a) $\text{HC}\equiv\text{C}-\text{C}(\text{CH}_3)_2\text{Cl}$, DMF, K_2CO_3 , KI, 65°C , N_2 , 14 h, 90%; (b) Zn/EtOH, rt 5 days, 98%; (c) NaH, DMSO, rt, 6 days, 29% (**210**), 43% (**253**); (d) MeI, K_2CO_3 , acetone, reflux, 11 h, 80%.

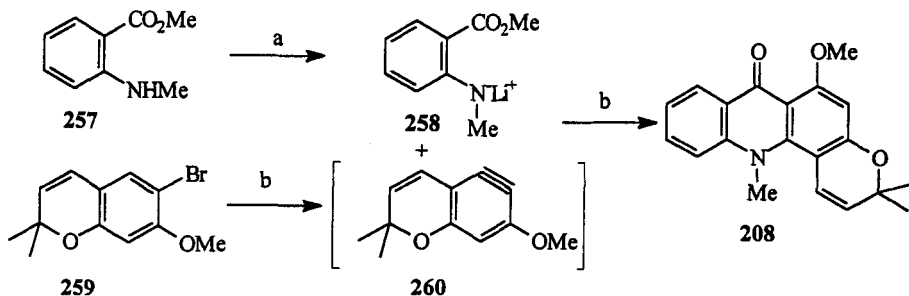
obtain 5,6-dihydro-6-demethoxyacronycine **256**. Dehydrogenation with DDQ provided 6-demethoxyacronycine **246** (Scheme 43).

Watanabe *et al.* (84CPB1264) have reported a one-step synthesis of acronycine **208**. Lithium methyl(2-methoxycarbonyl)phenyl amide **258** generated from methyl *N*-methylantranilate **257** *in situ* in the presence of excess lithium cyclohexylamide (LCA), was reacted with 6-bromo-2,2-dimethyl-7-methoxychromene **259** to produce acronycine **208**. A benzyne intermediate **260** is believed to be involved in this reaction (Scheme 44).

A regioselective synthesis of acronycine **208** from 3-acetyl-4-chloro-2-cyanomethylquinoline **261** has been described by Anand and Sinha (Scheme 45) [90H1733; 91JCS(P1)2339]. This synthesis involves alkylation of the cyanomethylene **261** with 1-bromo-3-methylbut-2-ene, methanolysis of the resulting nitrile **262** to give the ester **263**, and finally, ring closure and hydroxy-dechlorination to afford norglycocitrine II **264**. Oxidative cyclization of this acridone **264** with DDQ gave de-*N*-methylnoracronycine **211**,

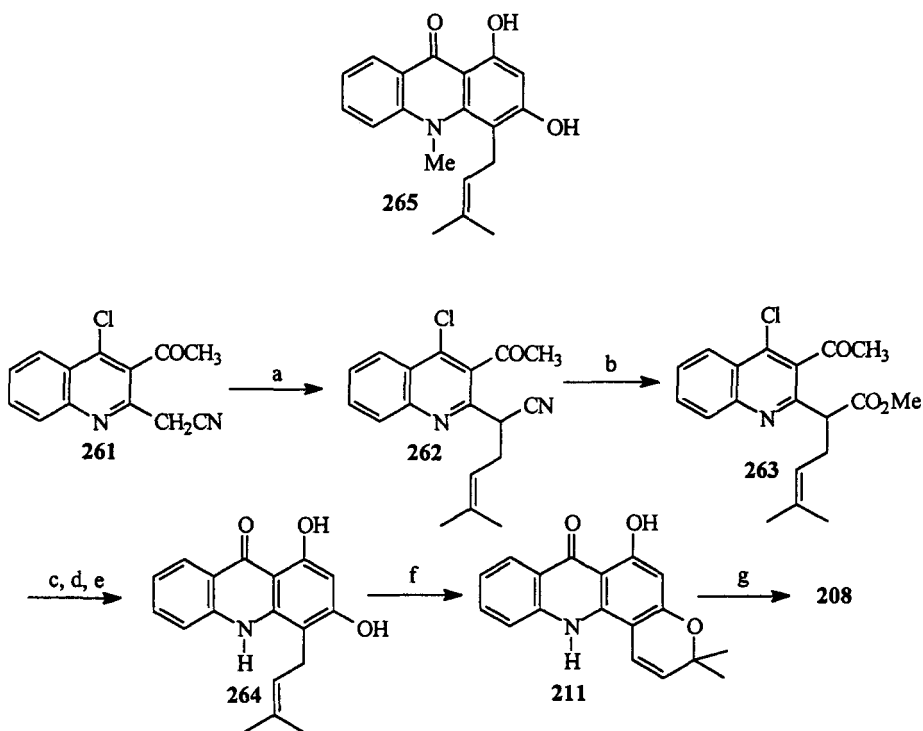


SCHEME 43. (a) LDA, THF, N_2 , -65°C , 56%; (b) DDQ, 88%.



SCHEME 44. (a) LCA, THF, N_2 , $-78^\circ C$; (b) LCA, THF, N_2 , $-10^\circ C$, 41% (a,b).

which was converted to acronycine **208** by methylation with methyl iodide. In another reaction, glycocitrine II **265** was converted to noracronycine **209** by oxidative cyclization with benzeneselenenyl chloride followed by hydrogen peroxide [83JCS(P1)1681].

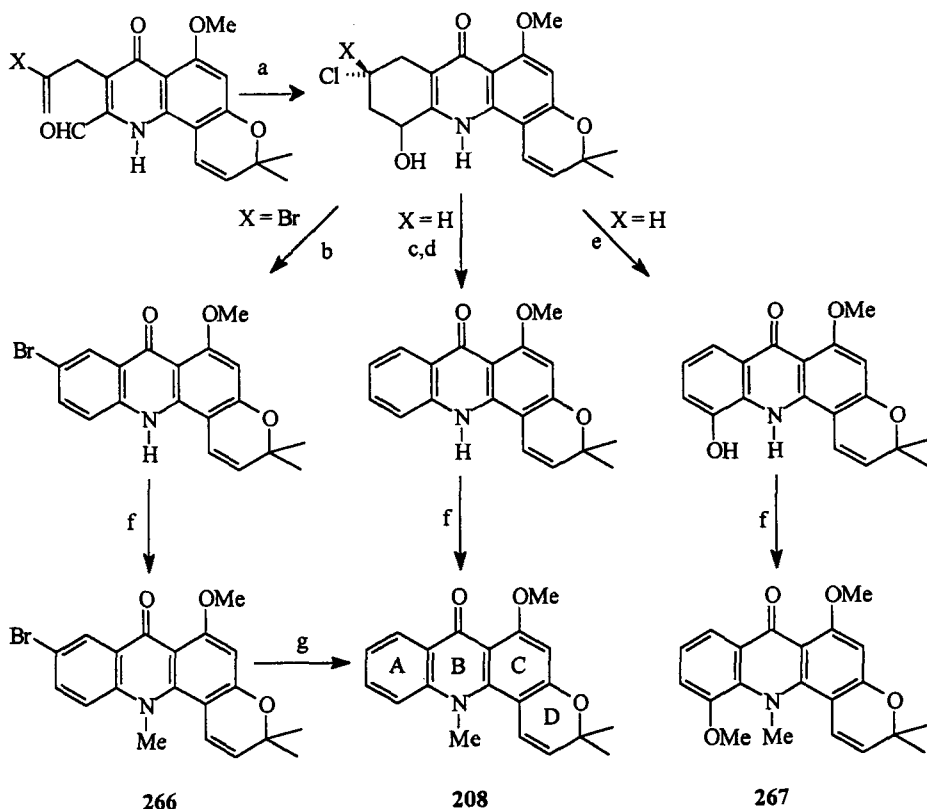


SCHEME 45. (a) $(CH_3)_2C=CHCH_2Br$, K_2CO_3 , DMF, reflux, 30 h, 48%; (b) MeOH, HCl, 70%; (c) NaH, THF, 3 h; (d) PhOH, $100^\circ C$, 3 h; (e) HCl, MeOH, 10 h, 47% (c,d,e); (f) DDQ, toluene, 52%; (g) NaH, DMF, MeI, 85%.

The syntheses of acronycine **208** and its derivatives, such as **266**, **267** reported by Blechert *et al.*, have novelty in that they involve the formation of ring "A" (Scheme 46) (78CB439; 80LA503).

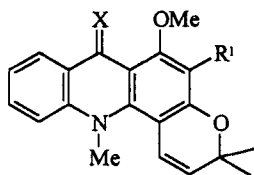
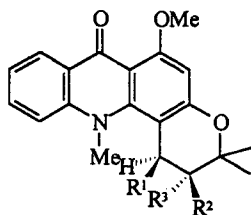
Microbial conversions of acronycine **208** to its hydroxy derivatives have been reported by two research groups (74JMC599, 74JMC653). Among many microbial agents, *Aspergillus alleaceus*, *Cunninghamella echinulata*, and *Streptomyces spectabilis* are found to be effective.

The reaction of organolithium compounds with noracronycine provided 7-substituted derivatives [95JCS(P1)511]. The reaction of acronycine with P_4S_{10} produced the thio analog **268** (79JPS36; 82S493), and oxidation of acronycine **208** resulted in one or more products that include acronycine epoxide **224**, 1-hydroxy-2-oxo-1,2-dihydroacronycine **269**, *cis*-1,2-dihydroxy-1,2-dihydroacronycine **270**, and 5-hydroxyacronycine **271**, de-

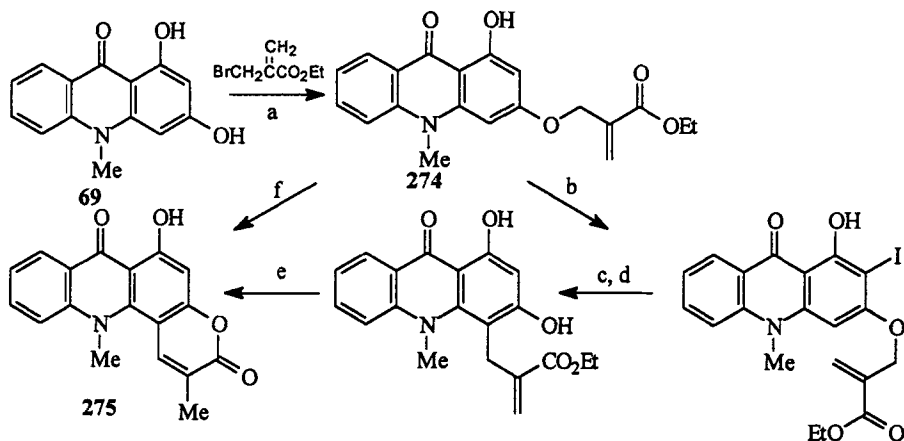


SCHEME 46. (a) $TiCl_4$, CH_2Cl_2 , rt 2 h, 60% (X = Br); (b) heat, 16%; (c) Ac_2O ; (d) $tBuOK$; (e) DMSO, pyridine, TFA, DCC, rt 20 h; (f) MeI, K_2CO_3 , acetone, 68% (X = Br); (g) BuLi, ether, 0°C, 4 h, 38%.

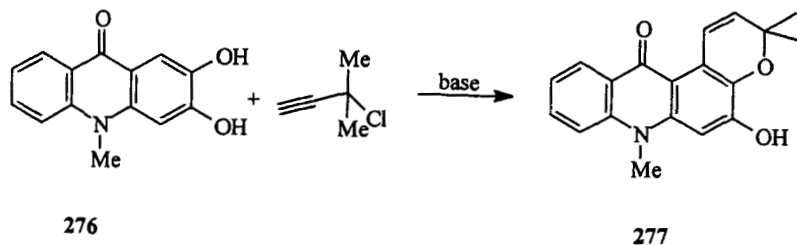
pending on the nature of the oxidizing agent (86JNP1091; 90M709; 94LA317, 94M731). The synthesis of 1-hydroxy-1,2-dihydroacronycine **272** and 2-hydroxy-1,2-dihydroacronycine **273** from acronycine **208** has also been reported (88MI2).

**268** X = S; R¹ = H**271** X = O; R¹ = OH**269** R¹ = OH; R²R³ = O**270** R¹ = R² = OH; R³ = H**272** R¹ = OH; R² = R³ = H**273** R¹ = R² = H; R³ = OH

Reisch and Gunaherath [89JCS(P1)1047] have reported the synthesis of 2,12-dimethyl-6-hydroxypyrano[2,3-*c*]acridine-3,7(12*H*)-dione **275** by two different routes starting from the alkylation of 1,3-dihydroxy-10-methylacridin-9(10*H*)-one **69** to give the α,β -unsaturated ester **274** (Scheme 47).



SCHEME 47. (a) K₂CO₃, acetone, reflux, 2 h, 73%; (b) I₂, HIO₄ (aq.), EtOH, rt, 2 h, 90%; (c) Ac₂O, pyridine, 100°C, 3 h, 32%; (d) K₂CO₃, MeOH, reflux, 15 min, 77%; (e) PEG, 200°C, 30 min, 71%; (f) PEG, 220°C, 15 min, 45%.



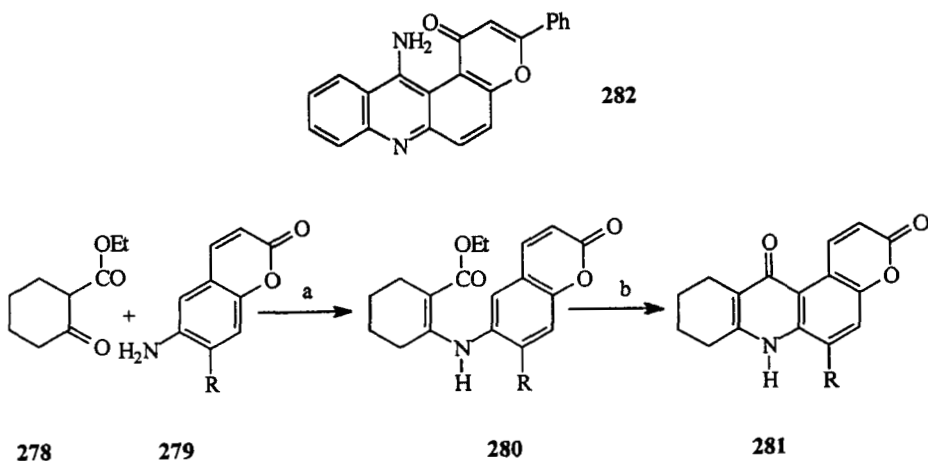
SCHEME 48

C. PYRANO[3,2-*a*]ACRIDINES

The coupling of 2,3-dihydroxy-10-methylacridin-9(10H)-one **276** with 3-chloro-3-methylbut-1-yne afforded a pyrano[3,2-*a*]acridine **277** (Scheme 48) (83MI1).

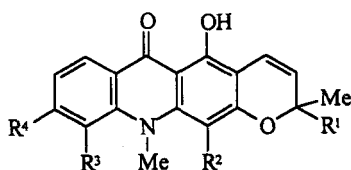
6-Aminobenzopyran-2-ones **279** undergo the Conrad-Limpach reaction with 2-ethoxycarbonylcyclohexanone **278** to give anils **280**, which, on heating in diphenyl ether at reflux, give cyclized products **281** (Scheme 49) (83JHC775).

We have prepared a series of pyrano[3,2-*a*]acridines (e.g., **282**) by the route described in Scheme 34, but using 6-oxo-5,6,7,8-tetrahydroflavone instead of 7-oxo-5,6,7,8-tetrahydroflavone (84TH1).

SCHEME 49. (a) Xylene, reflux, 29–30%; (b) Ph₂O, heat, 52%.

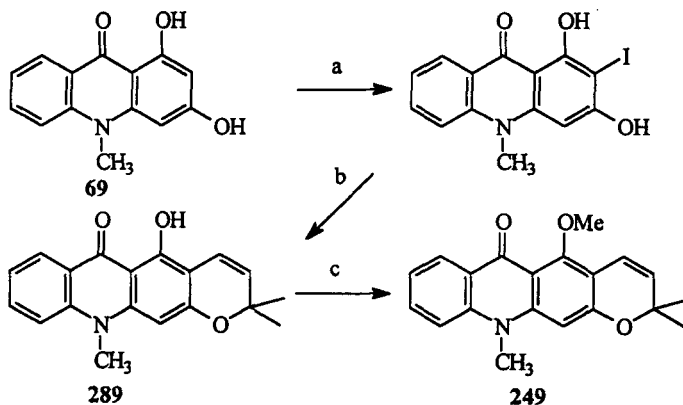
D. PYRANO[3,2-*b*]ACRIDINES

Linear pyranoacridines are very rare in nature. Only a few acridone alkaloids based on the pyrano[3,2-*b*]acridine ring system have been isolated and characterized. These include pyranofoline **283** and glycofoline **284** from *Glycosmis citrifolia* (Willd.) Lindl. [83JCS(P1)1681], honyumine **285** from *Citrus grandis* (86H41) and *Citrus funadoko* [90JCS(P1)1593], junosidine **286** from *Citrus junos* Tanaka (87H2077), and yukocitrine **287** from *Citrus yuko* Hort plant (92H2123) and, with 4-(2'-hydroxy-3'-methylbut-3'-enyl)-yukocitrine **288**, from *Bosistoa transversa* (96P235). Isoacronycine **249** or its de-*N*-methyl or de-*O*-methyl precursors have been separated as side products in most of the acronycine **208** syntheses (see pyrano[2,3-*c*]acridines).



- 283** $R^1 = \text{Me}; R^2 = \text{OMe}; R^3 = \text{OH}; R^4 = \text{H}$
284 $R^1 = \text{Me}_2\text{C}=\text{CHCH}_2; R^2 = R^4 = \text{H}; R^3 = \text{OH}$
285 $R^1 = \text{Me}; R^2 = \text{H}; R^3 = \text{OMe}; R^4 = \text{OH}$
286 $R^1 = \text{Me}; R^2 = R^4 = \text{H}; R^3 = \text{OMe}$
287 $R^1 = \text{Me}; R^2 = R^4 = \text{H}; R^3 = \text{OH}$
288 $R^1 = \text{Me}; R^2 = \text{CH}_2 = \text{C}(\text{CH}_3)\text{CH}(\text{OH})\text{CH}_2;$
 $R^3 = \text{OH}; R^4 = \text{H}$

Reisch *et al.* (91LA685) have reported a regioselective synthesis of isoacronycine **249** from 1,3-dihydroxy-10-methylacridin-9(10*H*)-one **69** that involves iodination at C-2, followed by palladium-catalyzed Heck condensation with 3-hydroxy-3-methylbut-1-ene to give isonoracronycine **289**. Methylation of isonoracronycine **289** with MeI gave isoacronycine **249** (Scheme 50).



SCHEME 50. (a) I_2 , H_5IO_6 , EtOH, rt, 92%; (b) $\text{Pd}(\text{OAc})_2$, $(n\text{Bu})_4\text{N}^+\text{Br}$, $\text{CH}_2=\text{CH}-\text{C}(\text{OH})(\text{Me})_2$; NaHCO_3 , DMSO/DMF, N_2 , 80°C, 36 h, 48%; (c) MeI, NaH, THF, 12 h, 80%.

We have prepared a linear pyranoacridine **291** by the condensation of *N*-benzyl anthranilonitrile with 7-oxo-5,6,7,8-tetrahydroflavone **200**, followed by base-catalyzed cyclization of the resultant enamine **290** (Scheme 51) (94TH1).

IV. Pyrroloacridines

Pyrroloacridines have been scarcely reported in the literature; only a few ring systems have been described.

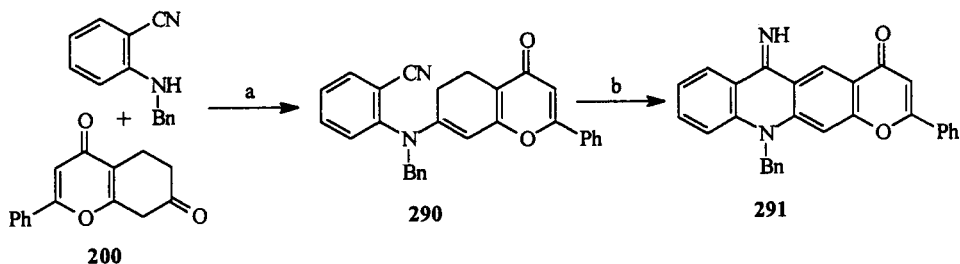
A. PYRROLO[2,3-*b*]ACRIDINES

Bilgic and Young have reported the formation of the benzo[*j*]pyrrolo[2,3-*b*]acridine **294** in a reaction between 1-(*N,N*-dimethylaminomethyl)naphth-2-ol **292** and 5-aminoindole. A quinone methide **293** is believed to be involved as an intermediate (Scheme 52). The reaction of the naphthol **292** with 5-aminoindazole gave the angular pyrazoloacridine **295** [80JCS(P1) 1233].

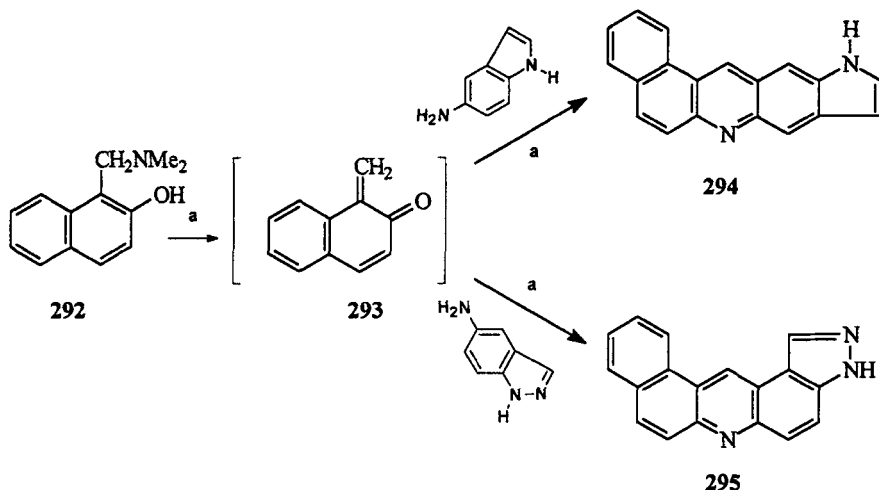
B. PYRROLO[2,3-*c*]ACRIDINES

Takagi *et al.* have synthesized a number of 4,5-dihydropyrrolo[2,3-*c*]acridines **297** from 4-oxo-4,5,6,7-tetrahydroindoles **296** (Scheme 53) (73BSF2807). Syntheses of condensed heterocyclic compounds based on 4-oxotetrahydroindoles have also been reported in the Russian literature (75MI1).

Another strategy involves the fusion of a pyrrole ring onto the acridine nucleus. The Japp-Klingemann reaction of the diazonium salt **298** of 3-



SCHEME 51. (a) PTSA, toluene, reflux; (b) LDA, THF, N₂, -78°C.

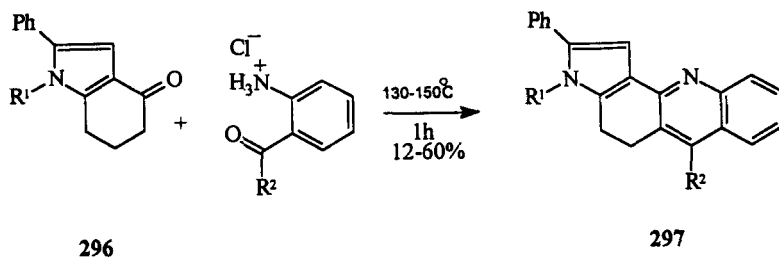


SCHEME 52. (a) Ph_2O , N_2 , reflux, 16 h, 67% **294**, 61% **295**.

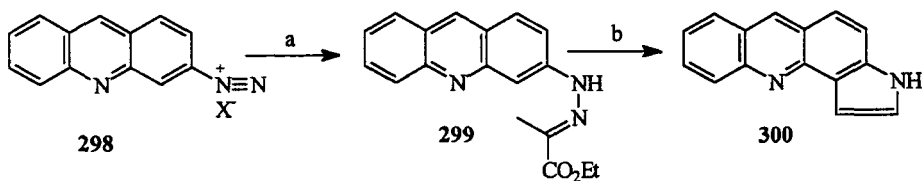
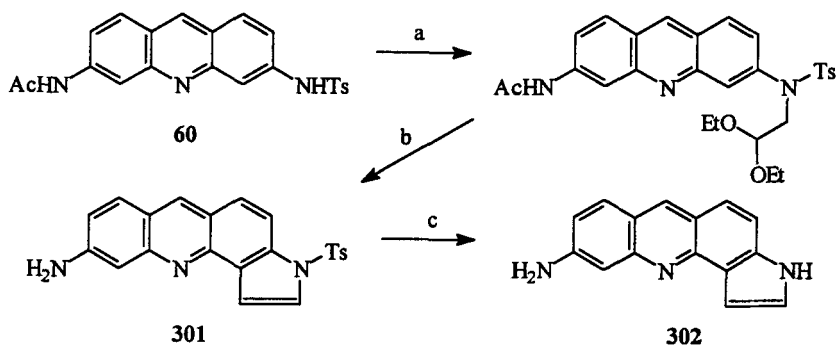
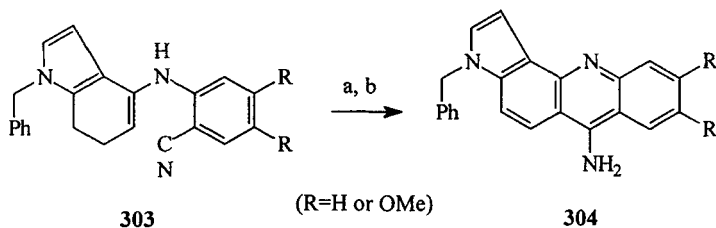
aminoacridine with ethyl 2-methylacetoacetate provided a hydrazone **299**, which was cyclized to pyrrolo[2,3-*c*]acridine **300** in the presence of ZnCl_2 (Scheme 54) (78KGS1277; 79KGS1092).

Wardani and Lhomme (93TL6411) used a different pathway for the construction of the pyrrole ring. Base-catalyzed alkylation of *N*-acetyl-*N'*-tosylproflavine **60** with bromoacetaldehyde diethyl acetal, followed by deprotection of the acetal function with concomitant ring closure and deacylation in acidic media yielded 9-amino-3-tosylpyrrolo[2,3-*c*]acridine **301**. Detosylation was achieved by basic hydrolysis to give 9-aminopyrrolo[2,3-*c*]acridine **302** (Scheme 55).

We have prepared pyrrolo[2,3-*c*]acridines **304** by our standard method, involving the base-catalyzed cyclization of the enamines **303**, followed by oxidation (Scheme 56) (96TH1).



SCHEME 53. $\text{R}^1 = \text{H}, \text{Me}, \text{Et}, \text{Ph}, p\text{-An}, \beta\text{-Naph}$; $\text{R}^2 = \text{Me}, \text{Ph}$.

SCHEME 54. (a) Ethyl 2-methylacetoacetate/base, 51%; (b) ZnCl₂.SCHEME 55. (a) DMF, K₂CO₃, BrCH₂CH(OEt)₂, 80°C, 4 days; (b) CH₃SO₃H/CH₂Cl₂ (1:9) reflux, 24 h, 40% (a,b); (c) KOH; DMF-H₂O, 78°C, 5 h, 75%.SCHEME 56. (a) NaNH₂, DME; (b) MnO₂, DMF, reflux.

C. PYRROLO[2,3,4-*kl*]ACRIDINES

Three polycyclic alkaloids that contain this ring system as part of their structures, plakinidines A **78**, B **79**, and C **80**, were isolated from the marine sponge *Plakortis* sp. (see Section II,C,1 on pyrido[3,2-*c*]acridines).

Gellerman *et al.* (94T12959) have described the biomimetic synthesis of a pyrrolo[2,3,4-*kl*]acridine **305** (Scheme 57).

V. Thienoacridines

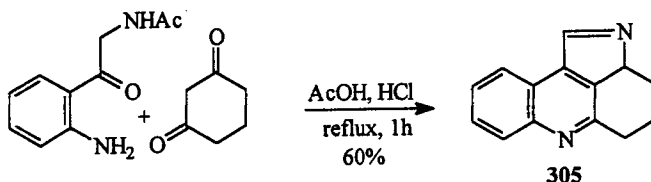
Only a few thienoacridine ring systems are known, and all are synthetic.

A. THIENO[2,3-*c*]ACRIDINES

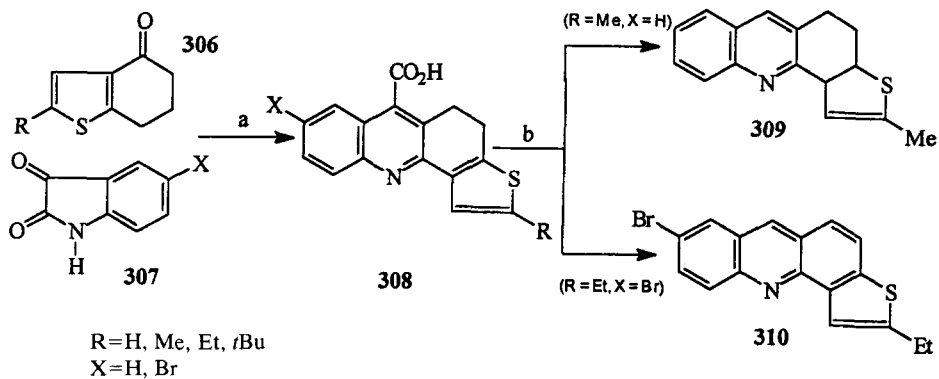
The Pfitzinger reaction of 6,7-dihydrobenzothiophen-4(5*H*)-ones **306** with isatins **307** produced 4,5-dihydrothieno[2,3-*c*]acridine-6-carboxylic acids **308** (Scheme 58) (50RTC1053; 55BSF1252, 55JCS21; 58JCS2418). Decarboxylation of the acid **308** (R = Me, X = H) upon heating above the melting point has been reported to give the dihydro derivative **309** (50RTC1053; 55BSF1252), and Buu-Hoi has reported the decarboxylation with concomitant dehydrogenation of the acid **308** (R = Et, X = Br) to give 6-bromo-2-ethylthieno[2,3-*c*]acridine **310** (Scheme 58) (58JCS2418).

Remers *et al.* (71JMC1127) have used a quite different approach, which involves the Vilsmeier–Haack formylation of 6,7-dihydrobenzothiophen-4(5*H*)-one **306** (R = H) followed by cyclocondensation with aniline to give 4,5-dihydrothieno[2,3-*c*]acridine **311** (Scheme 59).

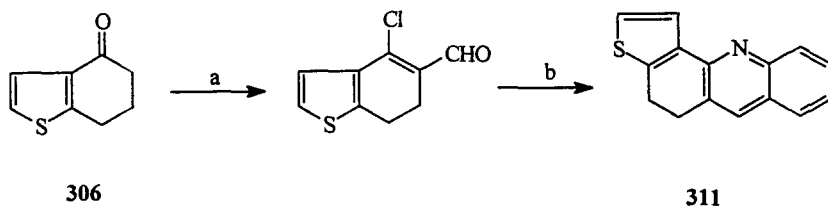
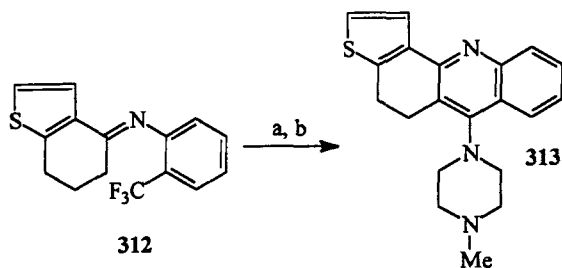
Strekowski *et al.* (90JOC4777) condensed the 6,7-dihydrobenzothiophen-4(5*H*)-one **306** (R = H) with 2-trifluoromethylaniline and then cyclized the resultant imine **312** with lithium 4-methylpiperazide to afford this ring system **313** (Scheme 60).

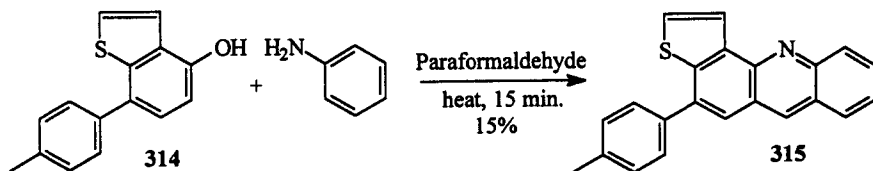


SCHEME 57



SCHEME 58. (a) KOH, EtOH, reflux, 10–24 h; (b) Heat > 300°C.

SCHEME 59. (a) POCl₃–DMF, 100°C, 1 h, 17%; (b) aniline, AcOH, reflux, 3 h, 67%.SCHEME 60. (a) Lithium 4-methylpiperazide, Et₂O, –10°C, 30 min; (b) H₃O⁺.

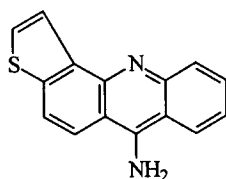


SCHEME 61

The Fetvadjan–Ullmann reaction between 4-hydroxy-7-(*p*-tolyl)benzothiophene **314**, aniline, and paraformaldehyde provides another pathway for the construction of thieno[2,3-*c*]acridines, such as **315** (Scheme 61) (81JHC1519).

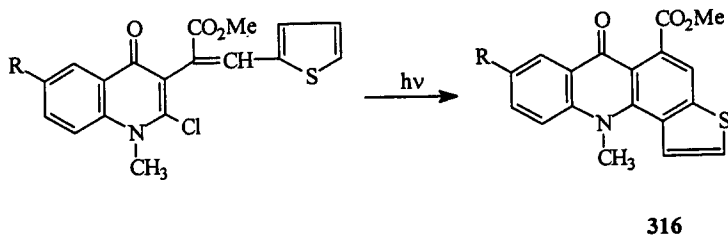
Suresh *et al.* (93SUL7) have described a novel route for the preparation of thieno[2,3-*c*]acridines **316** that involves photocyclization (Scheme 62).

We have used the strategy developed for the synthesis of pyrido[2,3-*c*]acridines to prepare thieno[2,3-*c*]acridines, such as **317** (96TH1).

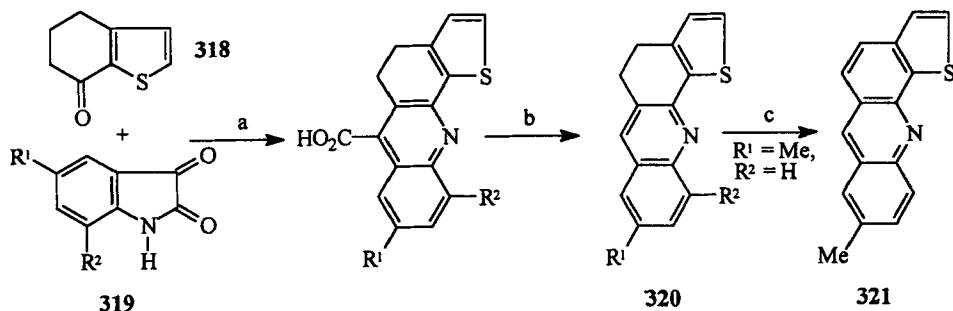
**317**

B. THIENO[3,2-*c*]ACRIDINES

Buu-Hoï and Royer (46CR806) obtained a series of thieno[3,2-*c*]acridines **320** by using the Pfitzinger reaction between 4,5-dihydrobenzothiophene-7(6*H*)-one **318** and isatins **319**, followed by decarboxylation at high temperature (Scheme 63). One of the decarboxylated products **320** ($\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$) was dehydrogenated with PbO at 310°C to give the fully aromatic system **321**.

**316**

SCHEME 62



SCHEME 63. $R^1 = H, Me, Br$; $R^2 = H, Me$. (a) KOH, EtOH; (b) heat; (c) PbO, 310°C.

C. THIENO[3,4-*c*]ACRIDINES

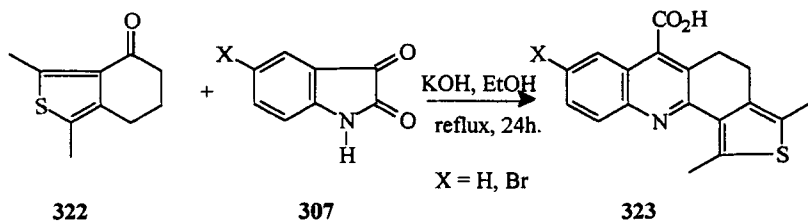
Isatins **307** on reaction with 1,3-dimethyl-6,7-dihydroisothiophene-4(5*H*)-one **322** gave 2,3-dimethyl-4,5-dihydrothieno[3,4-*c*]acridine-6-carboxylic acids **323** (Scheme 64) (50RTC1053).

VI. Furoacridines

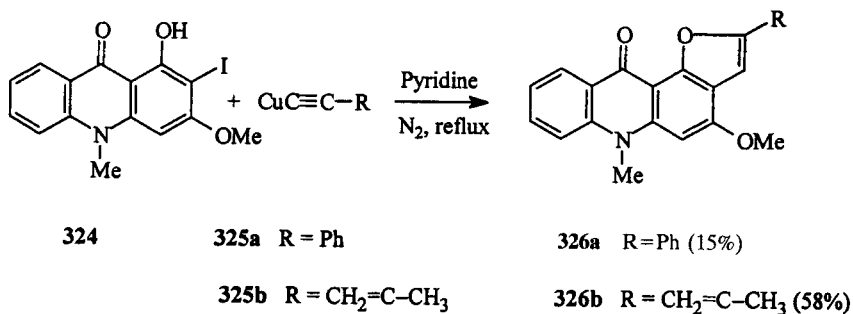
Only three furoacridine ring systems have been reported.

A. FURO[2,3-*a*]ACRIDINES

The reactions of copper(I) phenylacetylide **325a** and copper(I) isopropenylacetylide **325b** with 1-hydroxy-2-iodo-3-methoxy-10-methylacridin-9(10*H*)-one **324** gave furo[2,3-*a*]acridones **236a** and **236b** (Scheme 65) (84LA31).



SCHEME 64

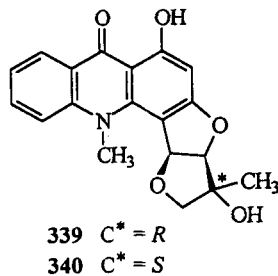
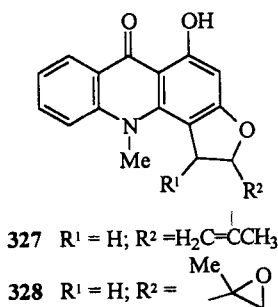


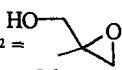

SCHEME 65

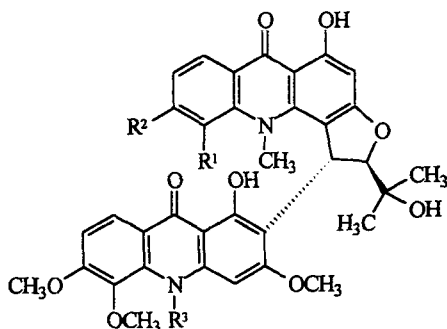
B. FURO[2,3-*c*]ACRIDINES

1. Isolation

This ring system is the basic skeleton of a number of acridone alkaloids isolated from intact plants or cell tissue cultures of various species from the Rutaceae family. Most of the dihydrofuroacridone alkaloids have been isolated from *Ruta graveolens*: rutacridone **327** (67MI1; 81MI1; 87PHA67; 88MI1; 90PHA500; 91MI3), rutacridone epoxide **328** (81MI1, 81ZN200; 82ZN132; 85MI2; 87PHA67; 88MI1; 90PHA500; 91MI2), 20-hydroxyrutacridone epoxide **329** (82ZN132; 85MI2), 1-hydroxyrutacridone epoxide **330** (85MI2), gravacridonol **331** (81MI1; 85MI2), gravacridone chloride **332** (73P2359; 87PHA67; 88MI1), isogravacridone chloride **333** (77P151; 91MI1), gravacridondiol **334** (72P2121; 76MI1, 76P240), gravacridondiol acetate **335** (91MI2), gravacridondiol monomethyl ether **336** (72P2121), gravacridontriol **337** (76MI1, 76P240), gravacridonolchlorine **338** (72P2121, 72P2359), and rutagravin **339** (85MI2). Rutacridone **327** and its epoxide **328** have also been detected in *Boenninghausenia albiflora* (78P169).



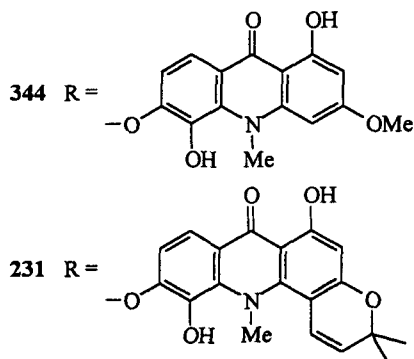
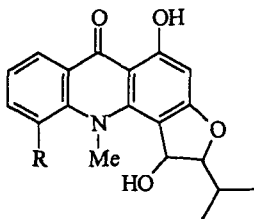
- 329 $R^1 = H$; $R^2 =$ 
- 330 $R^1 = OH$; $R^2 =$ 
- 331 $R^1 = H$; $R^2 = H_2C=CCH_2OH$
- 332 $R^1 = H$; $R^2 = H_3CC(Cl)CH_2OH$
- 333 $R^1 = H$; $R^2 = H_3CC(OH)CH_2Cl$
- 334 $R^1 = H$; $R^2 = H_3CC(OH)CH_2OH$
- 335 $R^1 = H$; $R^2 = H_3CC(OH)CH_2OAc$
- 336 $R^1 = H$; $R^2 = H_3CC(OH)CH_2OMe$
- 337 $R^1 = H$; $R^2 = HOC(CH_2OH)_2$
- 338 $R^1 = H$; $R^2 = ClC(CH_2OH)_2$



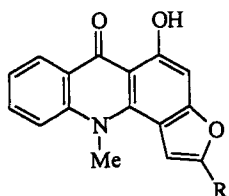
- 341 $R^1 = OH$; $R^2 = R^3 = H$
- 342 $R^1 = OMe$; $R^2 = OH$; $R^3 = H$
- 343 $R^1 = OMe$; $R^2 = OH$; $R^3 = Me$

Some of these dihydrofuroacridones, **327**, **328**, **331**, **333**, **334**, and **337**, have been separated by Baumert *et al.* from the cell culture of *Thamnosma montana* (94MI1). They have also obtained the glucosides of gravacridonol, gravacridondiols, and gravacridontriols. The last two glucosides were also isolated from roots and tissue culture of *Ruta graveolens* (76MI1, 76P240).

Three bisacridone alkaloids, citbisamines A **341**, B **342**, and C **343**, containing a C—C bond linkage between the dihydrofuroacridone and the acridone ring systems, have been isolated by Takemura *et al.* from the roots of Marsh grapefruit (*Citrus paradisi*) and Hirado-buntan (*Citrus grandis*) (95CPB1340). Previously, Fraser and Lewis reported the isolation of two dimeric alkaloids (containing *O*-linkages), atalanine **344** and ataline **231**, from *Atlantia ceylanica* [73JCS(CC)615].



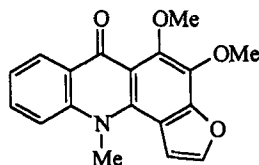
A fully dehydrogenated furoacridine (furacridone = furofoline-I) **345** was detected for the first time in *Ruta graveolens* by Reisch *et al.* (77P151) as a mixture with 1-hydroxy-3-methoxy-10-methylacridin-9(10*H*)-one. Wu *et al.* [83JCS(P1)1681] were able to isolate furofoline-I **345** and furofoline II **346** from *Glycosmis citrifolia* (willd.) Lindl.



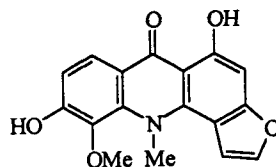
345 R = H

346 R = C(OH)Me₂

347 R = COMe



348



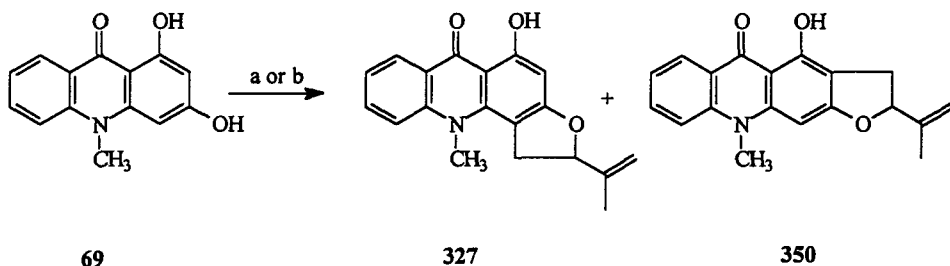
349

Hallacridone **347** was isolated from *Ruta graveolens* by Baumert *et al.*, along with the dihydrofuroacridones **327**, **328**, and **332** (87PHA67; 88MI1). Its structure was revised by Reisch and Gunaherath [89JCS(P1)1047] on the basis of spectroscopic evidence and total synthesis. It was also isolated from tissue cultures of *Ruta graveolens* (90PHA500) and *Thamnosma montana* (94MI1). Isolation of two new alkaloids, thehaplosine **348** (93MI2) and furoparadine **349** (95H187), has been achieved from the aerial parts of *Halophyllum thesioides* and roots of Marsh grapefruit (Rutaceae), respectively.

2. Syntheses

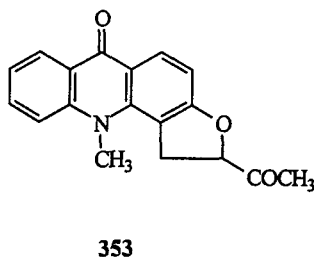
Rutacridone **327** was synthesized for the first time by Mester *et al.* (81H77) by base-catalyzed alkylation, with concomitant cyclization, of 1,3-dihydroxy-10-methylacridin-9(10*H*)-one **69** with 1,4-dibromo-2-methylbut-2-ene. The linear isomer, isorutacridone **350**, was also obtained as a by-product (Scheme 66). A better yield of rutacridone **327** was obtained when Al₂O₃ was used as the catalyst (90M829). Once again, isorutacridone **350** was obtained as a by-product (Scheme 66).

Maier *et al.* have observed that microsomes (from *Ruta graveolens* cell cultures) catalyze the condensation of 1,3-dihydroxy-10-methylacridin-9(10*H*)-one **69** with isopentenyl pyrophosphate or dimethylallyl pyrophosphate, in the presence of NADPH and O₂, to produce rutacridone **327**, and also that the reaction involved glycositrine-II **265** as an intermediate (90MI2; 93P691). A possible precursor **351** of rutacridone **327** has also been isolated from a reaction of glycositrine-II **265** with *m*-chloroperbenzoic acid (MCPBA) (Scheme 67) (93CPB383).

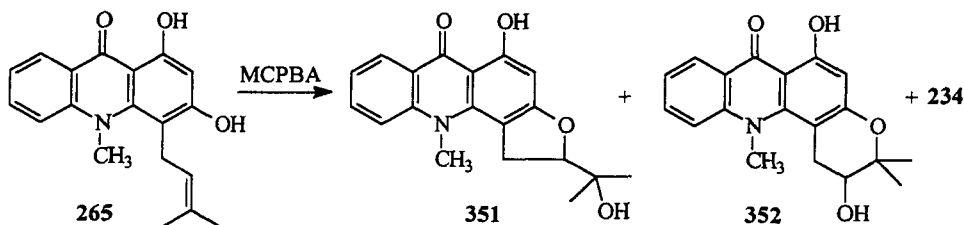


SCHEME 66. (a) Na, MeOH, $\text{BrCH}_2\text{CH}=\text{C}(\text{CH}_3)\text{CH}_2\text{Br}$, 15.5% (**327**), 5.2% (**350**); (b) Al_2O_3 , $\text{ClCH}_2\text{CH}=\text{C}(\text{CH}_3)\text{CH}_2\text{Br}$.

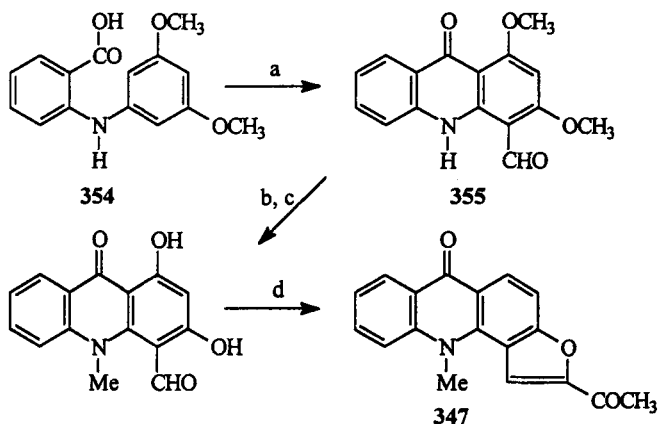
Selective hydroxylation of rutacridone **327** with SeO_2 in the presence of *t*BuOOH provided gravacridonol **331** (91LA299), and oxidation with KMnO_4 afforded rutagravin **339**, isorutagravin **340**, gravacridondiol **334**, and dihydrohallacridone **353** [69CI(L)1809]. Dehydrogenation of dihydrohallacridone with DDQ produced hallacridone **347** [94JCR(S)157].



To confirm its structure, Reisch *et al.* have synthesized hallacridone **347** (Scheme 68) [89JCS(P1)1047]. Ullmann-amine coupling of 2-chlorobenzoic acid and 3,5-dimethoxyaniline gave an amine **354** that, on treatment with DMF-POCl_3 , provided 4-formyl-1,3-dimethoxyacridin-9(10*H*)-one **355**. *N*-Methylation, *O*-demethylation, and subsequent condensation with 1-chloropropan-2-one in basic media gave hallacridone **347**.

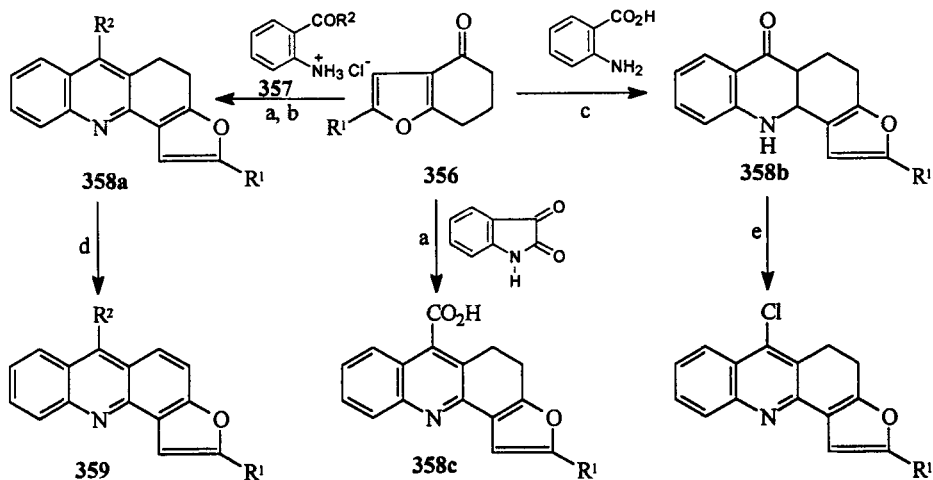


SCHEME 67

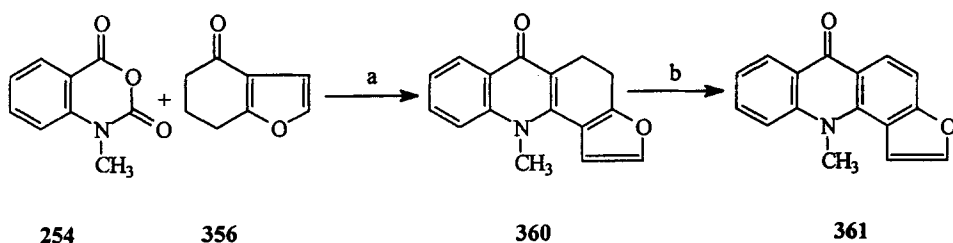


SCHEME 68. (a) POCl_3 , DMF, rt, 1.5 h, 15%; (b) MeI, Ag_2O , DMF, 16 h, 76%; (c) BCl_3 , CH_2Cl_2 , rt 72 h, 64%; (d) $\text{ClCH}_2\text{COCH}_3$, K_2CO_3 , acetone, reflux, 2 h, 50%.

Takagi and Ueda have prepared a number of 4,5-dihydrofuro[2,3-*c*]acridines **358a–c** from 4,5,6,7-tetrahydrobenzofuran-4-ones **356** by condensing with isatin, anthranilic acid, and 2-aminophenylcarbonyl hydrochlorides **357** using a range of conditions (Scheme 69) (71CPB1218; 72CPB380,



SCHEME 69. $\text{R}^1 = \text{Me, Ph, } p\text{MeO-Ph, } p\text{Br-Ph}$; $\text{R}^2 = \text{Me, Ph}$. (a) KOH , EtOH, reflux, 50–64 h, 18–31% (**358c**); (b) heat 110–140°C, 1 h, 40–71%, (a,b); (c) 120–200°C, 1 h, 16–38%; (d) Pd/C , 260–290°C, 15 min, 40–54%; (e) POCl_3 , 135°C, 2 h, 71%.



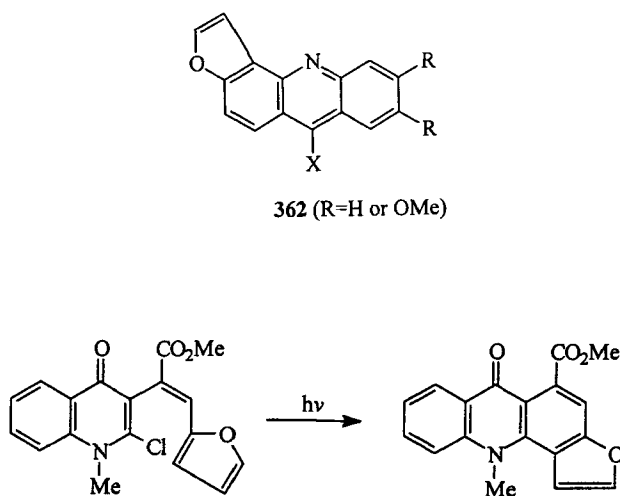
SCHEME 70. (a) LDA, -65 to -40°C , 2 h, 67%; (b) DDQ, toluene, 70°C , 15 min., 100%.

72CPB2051). Dehydrogenation of 4,5-dihydrofuro[2,3-*c*]acridines **358** has also been reported to give the aromatic systems **359**.

Coppola (84JHC1569) condensed *N*-methylisatoic anhydride **254** with the lithium enolate of 4,5,6,7-tetrahydrobenzofuran-4-one **356** ($R = \text{H}$) and obtained *N*-methylfuro[2,3-*c*]acridin-6-one **361** after dehydrogenation of the resultant 4,5-dihydrofuroacridone **360** (Scheme 70).

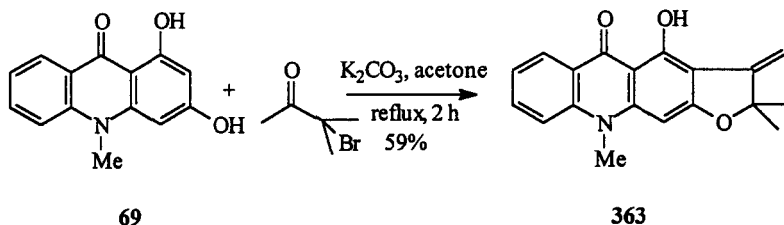
The method of Jayabalan and Shanmugan is novel in that it involves the construction of a ring between a quinoline and furan moieties to complete this skeleton (Scheme 71) (91ZN558).

Once again, we have used the strategy developed for the synthesis of pyrido[2,3-*c*]acridines to prepare furo[2,3-*c*]acridines **362** (96TH1).



362 ($R = \text{H}$ or OMe)

SCHEME 71



SCHEME 72

C. FURO[3,2-*b*]ACRIDINES

Reisch and co-workers have isolated isorutacridone **350** as a by-product during their base-catalyzed (81H77) and Al_2O_3 -catalyzed (90M829) synthesis of rutacridone **327** (Scheme 66). They observed that the use of an ion-exchange resin as the catalyst favored the formation of isorutacridone **350** as the major product (81H77). The same group also reported the formation of another linear furoacridine, 4-hydroxy-3-methylene-2,2,10-trimethyl-2,3-dihydrofuro[3,2-*b*]acridin-5(10*H*)-one **363** (Scheme 72) (89JHC1849).

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The Chemistry of C-Nucleosides and Their Analogs II: C-Nucleosides of Condensed Heterocyclic Bases

MOHAMMED A. E. SHABAN

*Department of Chemistry, Faculty of Science, Alexandria University,
Alexandria 21321, Egypt*

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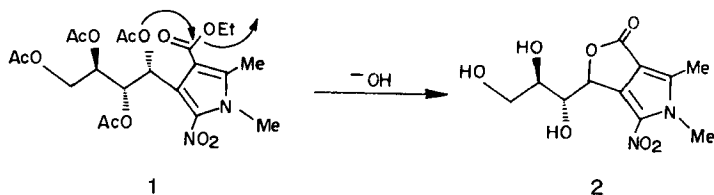
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C. Pyrrolo[3,2- <i>d</i>]pyrimidine Acyclo C-Nucleosides	223
D. Furo[3,2- <i>d</i>]pyrimidine C-Nucleosides	224
E. Thieno[3,2- <i>d</i>]pyrimidine C-Nucleosides	226
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G. Thieno[3,4- <i>d</i>]pyrimidine C-Nucleosides	227
H. Pyrazolo[1,5- <i>a</i>]pyrimidine C-Nucleosides	227
I. Pyrazolo[3,4- <i>d</i>]pyrimidine C-Nucleosides	229
J. Pyrazolo[4,3- <i>d</i>]pyrimidine C-Nucleosides	230
K. Pyrazolo[4,3- <i>d</i>]pyrimidine Acyclo C-Nucleosides	247

L. Imidazo[1,2- <i>a</i>]pyrimidine Acyclo C-Nucleosides	248
M. Imidazo[4,5- <i>d</i>]pyrimidine C-Nucleosides	249
N. Imidazo[4,5- <i>d</i>]pyrimidine Acyclo C-Nucleosides	252
O. Isothiazolo[4,5- <i>d</i>]pyrimidine C-Nucleosides	254
P. Thiazolo- and Selenazolo[5,4- <i>d</i>]pyrimidine C-Nucleosides	255
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R. 1,2,4-Triazolo[1,5- <i>a</i>]pyrimidine C-Nucleosides	257
S. 1,2,4-Triazolo[1,5- <i>c</i>]pyrimidine C-Nucleosides	257
T. 1,2,4-Triazolo[1,5- <i>c</i>]pyrimidine Acyclo C-Nucleosides	258
U. 1,2,4-Triazolo[4,3- <i>a</i>]pyrimidine C-Nucleosides	259
V. 1,2,4-Triazolo[4,3- <i>a</i>]pyrimidine Acyclo C-Nucleosides	259
W. Quinazoline C-Nucleosides	260
X. Quinazoline Acyclo C-Nucleosides	260
Y. Pyrido[1,2- <i>a</i>]pyrimidine C-Nucleosides	261
Z. Pyrido[4,3- <i>d</i>]pyrimidine C-Nucleosides	262
A'. Pyrimido[4,5- <i>d</i>]pyrimidine Acyclo C-Nucleosides	262
B'. Pyrazino[2,3- <i>d</i>]pyrimidine C-Nucleosides	263
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B. Pyrrolo[1,2- <i>a</i>]pyrazine Acyclo C-Nucleosides	277
C. Imidazo[1,2- <i>a</i>]pyrazine C-Nucleosides	279
D. Imidazo[1,5- <i>a</i>]pyrazine C-Nucleosides	280
E. Oxazolo[3,4- <i>a</i>]pyrazine Acyclo C-Nucleosides	280
F. 1,2,4-Triazolo[4,3- <i>a</i>]pyrazine C-Nucleosides	281
G. Quinoxaline C-Nucleosides	282
H. Quinoxaline Acyclo C-Nucleosides	282
I. Pyrido[2,3- <i>b</i>]pyrazine Acyclo C-Nucleosides	284
J. Pyrrolo[1,2- <i>a</i>]quinoxaline C-Nucleosides	285
K. Furo[2,3- <i>b</i>]quinoxaline Acyclo C-Nucleosides	286
L. Furo[3,4- <i>b</i>]quinoxaline Acyclo C-Nucleosides	286
M. Pyrazolo[3,4- <i>b</i>]quinoxaline (Flavazole) C-Nucleosides	287
N. Pyrazolo[3,4- <i>b</i>]quinoxaline (Flavazole) Acyclo C-Nucleosides	288
O. Benzo[<i>f</i>]quinoxaline Acyclo C-Nucleosides	289
P. Benzo[<i>g</i>]quinoxaline Acyclo C-Nucleosides	290
Q. Pyrido[2,3- <i>c</i>]pyrazolo[3,4- <i>b</i>]pyrazine Acyclo C-Nucleosides	290
R. Benzo[<i>g</i>]pyrazolo[3,4- <i>b</i>]quinoxaline Acyclo C-Nucleosides	291
S. Benzo[<i>h</i>]pyrazolo[3,4- <i>b</i>]quinoxaline Acyclo C-Nucleosides	291
T. Benzo[<i>i</i>]pyrazolo[3,4- <i>b</i>]quinoxaline Acyclo C-Nucleosides	292
U. Quinoxalino[7',6':2,3]quinoxaline Acyclo C-Nucleosides	292
V. Pyrazolo[3,4- <i>b</i>]quinoxalino[7',6':2,3]quinoxaline Acyclo C-Nucleosides	292
XIII. Condensed Oxazine C-Nucleosides	293
A. Pyrrolo[3,2- <i>d</i>]oxazine C-Nucleosides	293
B. Pyrazolo[4,3- <i>d</i>]oxazine C-Nucleosides	293
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XIV. Condensed 1,2,3-Triazine C-Nucleoside	295
A. Thiazolo[5,4- <i>d</i>]1,2,3-triazine C-Nucleosides	295

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B. Pyrrolo[1,5- <i>d</i>]1,2,4-triazine C-Nucleosides	296
C. Imidazo[5,1- <i>f</i>]1,2,4-triazine C-Nucleosides	297
D. Imidazo[5,1- <i>f</i>]1,2,4-triazine Acyclo C-Nucleosides	298
E. 1,2,4-Triazolo[3,4- <i>f</i>]1,2,4-triazine C-Nucleosides	298
F. 1,2,4-Triazolo[4,3- <i>b</i>]1,2,4-triazine Acyclo C-Nucleosides	299
G. 1,2,4-Triazolo[3,4- <i>c</i>]1,2,4-triazine Acyclo C-Nucleosides	300
H. 1,2,4-Triazolo[3,4- <i>f</i>]1,2,4-triazine Acyclo C-Nucleosides	301
XVI. Condensed 1,3,5-Triazine C-Nucleosides	301
A. Pyrazolo[1,5- <i>a</i>]1,3,5-triazine C-Nucleosides	301
B. Pyrazolo[1,5- <i>f</i>]1,3,5-triazine Acyclo C-Nucleosides	303
C. Imidazo[1,5- <i>a</i>]1,3,5-triazine Acyclo C-Nucleosides	303
XVII. Condensed 1,4-Diazepine C-Nucleosides	305
A. Benzo[<i>b</i>]thiazolo[3,2- <i>d</i>]1,4-diazepine Acyclo C-Nucleosides	305
XVIII. Condensed 1,4-Oxazepine C-Nucleosides	305
A. Benzo[<i>b</i>]thiazolo[3,2- <i>d</i>]1,4-oxazepine Acyclo C-Nucleosides	305
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XX. Condensed 1,5-Thiazepine C-Nucleosides	306
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I. Introduction

The present review complements and concludes the first part [97-AHC(68)223], which was devoted to the chemistry of C-nucleosides of hetero monocyclic bases. C-Nucleosides reviewed in this part were systematized according to the size and complexity of the base component, starting with those of simpler base components followed by more complex ones. Within a class of a particular base component, the arrangement also goes from less to more complex attached components. The C-nucleosides of a certain category are discussed first, followed by their analogs in the sequence homo, carbocyclic, reverse, and acyclo C-nucleosides [for definitions, see Part I, 97AHC(68)223]. To avoid redundancy, whenever the synthesis of a C-nucleoside of a condensed base comprised the elaboration of a C-nucleoside of a monocyclic base, the synthesis of the latter is usually not discussed, since it has already been mentioned in the first part of this review. The literature has been surveyed to Vol. 125, No. 7 (1996), of *Chemical Abstracts* and Vol. 142 No. 10 (1996), of the *Index Chemicus*.



SCHEME 1

II. Condensed Azole C-Nucleosides

A. FURO[3,4-*c*]PYRROLYL ACYCLO C-NUCLEOSIDES

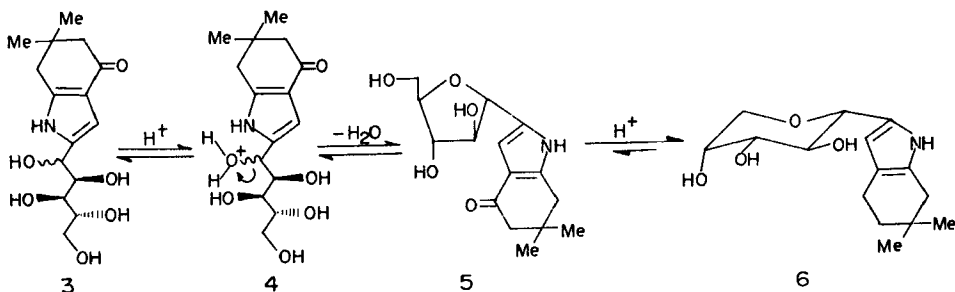
1. Furo[4,3-*c*]pyrrol-1-yl Acyclo C-Nucleosides

Base-catalyzed de-*O*-acetylation and deesterification of the 3-(tetra-*O*-acetyl-*D*-arabino-tetritol-1-yl)-4-ethoxycarbonyl-2,5-dimethyl-2-nitropyrrole **1** took place with concomitant γ -lactone ring formation to provide the furo[3,4-*c*]pyrrol-1-yl acyclo C-nucleoside **2** [85AQ(C)49] (Scheme 1).

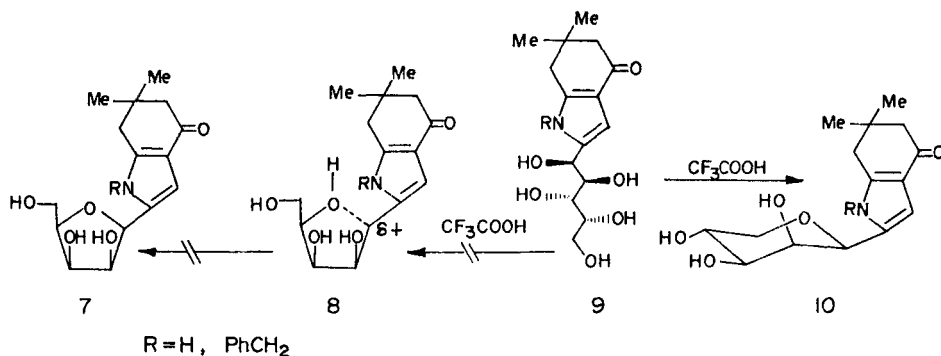
B. INDOLE C-NUCLEOSIDES

1. Indol-2-yl C-Nucleosides

Kinetically controlled acid-catalyzed cyclodehydration of the 2-(*D*-gluco- or *D*-manno-pentitol-1-yl)-4,5,6,7-tetrahydroindol-4-one (**3**) (Section II, C,1) furnished the 2-(α -*D*-arabinofuranosyl)-4,5,6,7-tetrahydroindol-4-one (**5**) [74JCS(P1)1237; 80MI5; 83MI9; 85MI10]. The furanose C-nucleoside **5** then was transformed to the thermodynamically more stable pyranose analog **6** (82MI5) (Scheme 2).



SCHEME 2



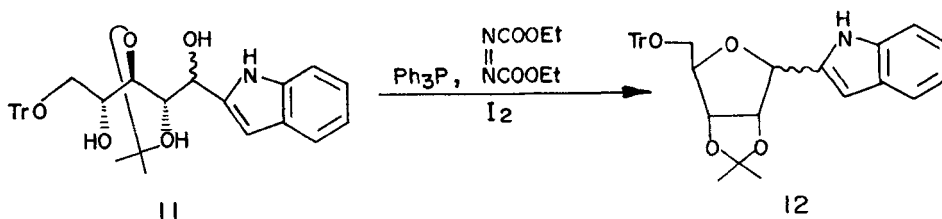
SCHEME 3

Dehydrative cyclization of the 2-(*D*-galacto-pentitol-1-yl) indol-4-one **9** directly gave the 2-(β -*D*-lyxopyranosyl)indol-4-one **10** without passing through the β -*D*-furanose C-nucleoside **7** because of steric destabilization of the transition state **8**, which contains the bulky CH_2OH , HO-2', and HO-3' groups residing on the same side of the new furan ring [80MI5; 83MI9] (Scheme 3). C-Nucleoside **10** inhibited growth of Ehrlich ascites tumor cells [81FA(36)733].

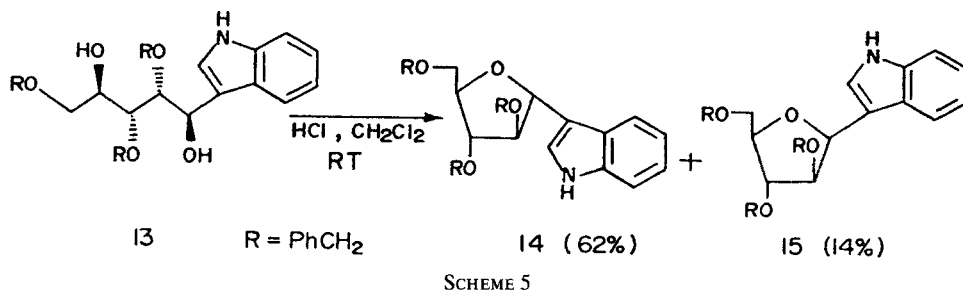
Cyclization of indol-2-yl acyclo C-nucleosides that carry acid-sensitive *O*-protective groups such as **11** has been successfully achieved without affecting these groups by dehydration with triphenylphosphine–diethyl azodicarboxylate–iodine; a mixture of anomeric C-nucleosides (**12**) was usually produced [94CL265; 95JAP(K)95/118268] (Scheme 4).

2. Indol-3-yl C-Nucleosides

Cyclization of the 3-(*D*-manno-pentitol-1-yl)indole derivative **13** (Section II,C,2) with dilute hydrochloric acid gave a mixture of the 3-(α - and β -*D*-arabinofuranosyl)indoles **14** and **15**; the α -anomer predominated (91JOC5466) (Scheme 5).



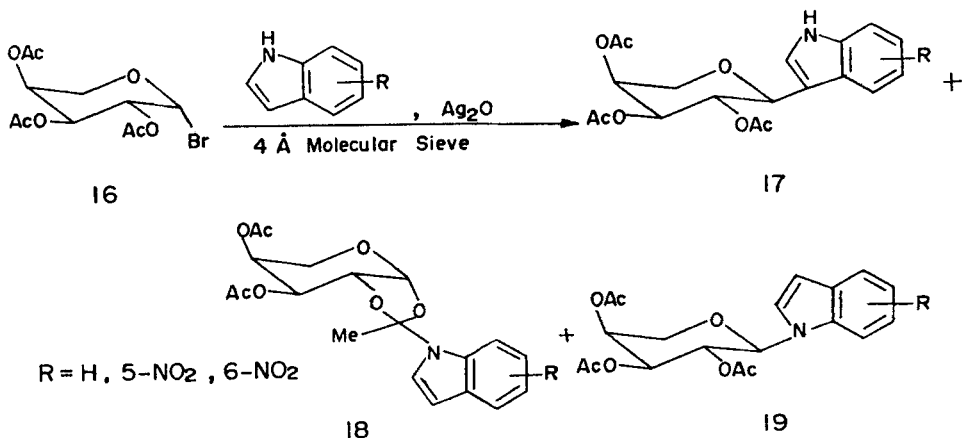
SCHEME 4

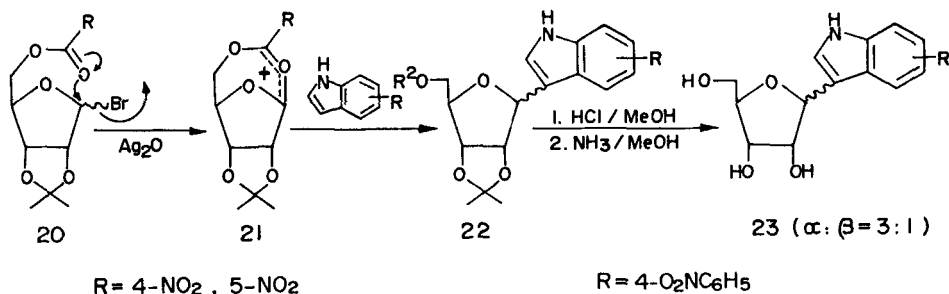


Glycosylation of indole with glycosyl halides in the presence of silver oxide was studied by Russian groups, who found that a glycosyl halide having a participating group at C2 such as **16** gave a mixture of one anomer of the indol-3-yl C-nucleoside **17**, the N-nucleoside **19**, and the *ortho* acid amide **18** (80MI7) (Scheme 6). Glycosyl halides without a participating group at C2 (e.g., **20**) gave a mixture of the two anomeric indol-3-yl C-nucleosides (**22**) in which the α -anomer preponderated (60MI1; 80KGS1423; 84MI4) (Scheme 7).

3. Indol-4-yl C-Nucleosides

Reaction of the C- β -D-ribofuranosylnitromethane **24** with 2-allyl-1-ethoxycarbonylpyrrole in the presence of phenyl isocyanate formed the isoxazoline **26**. Catalytic reduction of **26** produced the α -ketol **27**, which



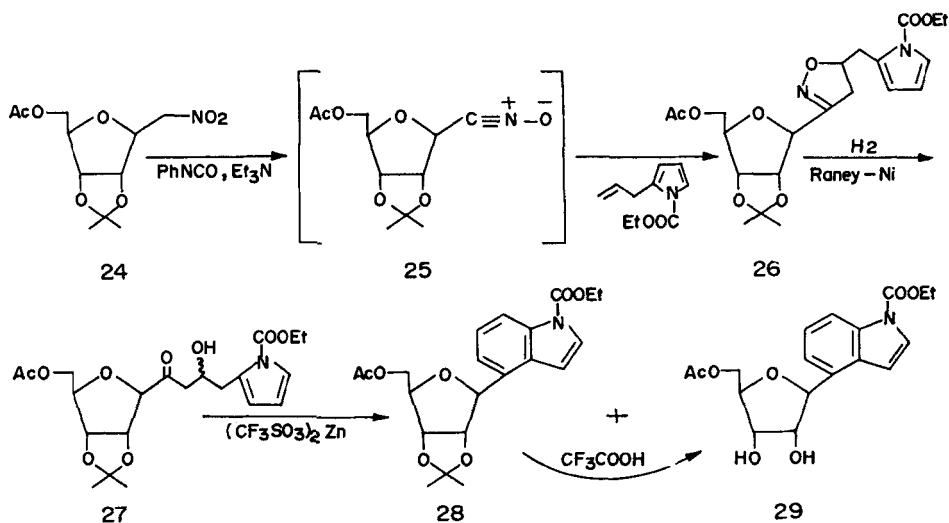


SCHEME 7

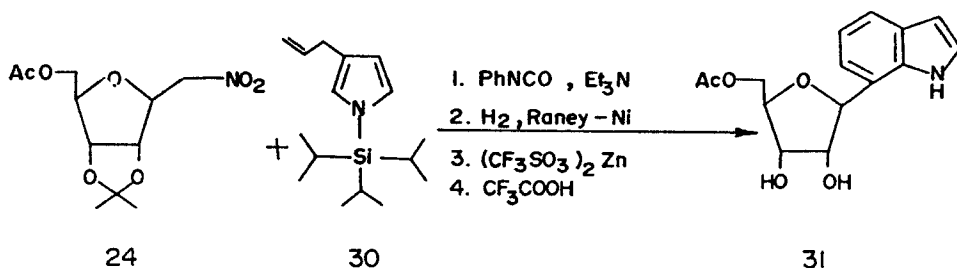
cyclized with Lewis acids to the indol-4-yl *C*-nucleoside **28** [87JCS(CC)680] (Scheme 8).

4. Indol-7-yl *C*-Nucleosides

Example **31** was obtained by reacting **24** with 3-allyl-1-(triisopropylsilyl)pyrrole **30** similarly to the preparation of **28** [87JCS(CC)680] (Scheme 9).



SCHEME 8



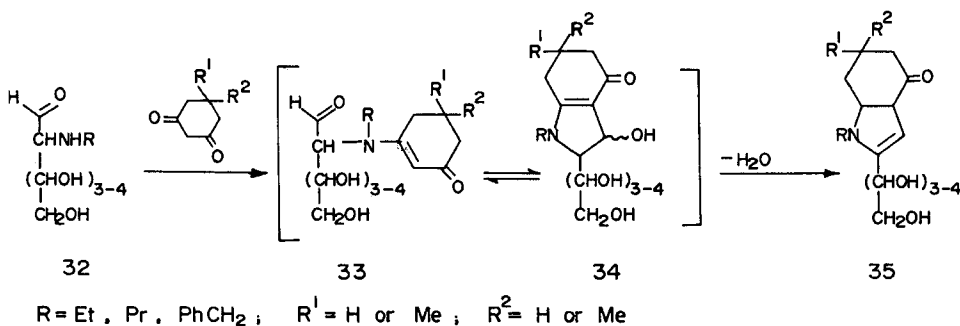
SCHEME 9

C. INDOLE ACYCLO C-NUCLEOSIDES

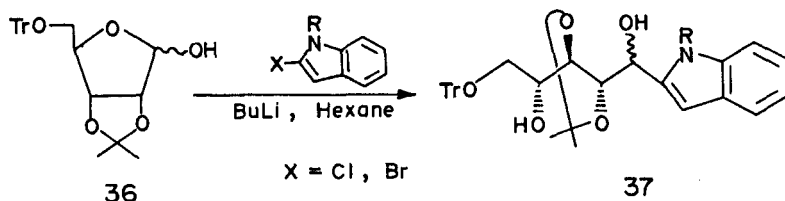
1. Indol-2-yl Acyclo C-Nucleosides

2-Amino-2-deoxyaldoses [66AQ(B)471; 74JCS(P1)1237; 80MI4; 85MI10] **32**, (R = H) and 2-alkylaminoaldoses (**32**, R = alkyl) (83MI9; 85MI7) cyclocondensed with cyclohexane-1,3-diones to produce 2-(alditol-1-yl)-1,5,6,7-tetrahydroindol-4-ones (**35**) (Scheme 10). Structures of the acyclo *C*-nucleosides **35** were proved by oxidation to the corresponding indol-2-carboxylic acids [66AQ(B)471]. Some 4-hydrazono derivatives of **35** were prepared (91MI1).

aldehydo-Sugar derivatives (e.g., **36**) reacted with 2-lithioindole to afford the indol-2-yl acyclo *C*-nucleosides (e.g., **37**) [94CL265; 95JAP(K)95/118268] (Scheme 11).



SCHEME 10



SCHEME 11

2. Indol-3-yl Acyclo C-Nucleosides

Trapping the saccharide carbene **40**, formed by copper-catalyzed thermal decomposition of 1-diazo-1-deoxyketose acetates (**39**), by 1-alkylindoles gave the acetylated 3-(2-ulose-1-yl)indoles **41** (67MI3; 68DOK849, 68MI3) (Scheme 12).

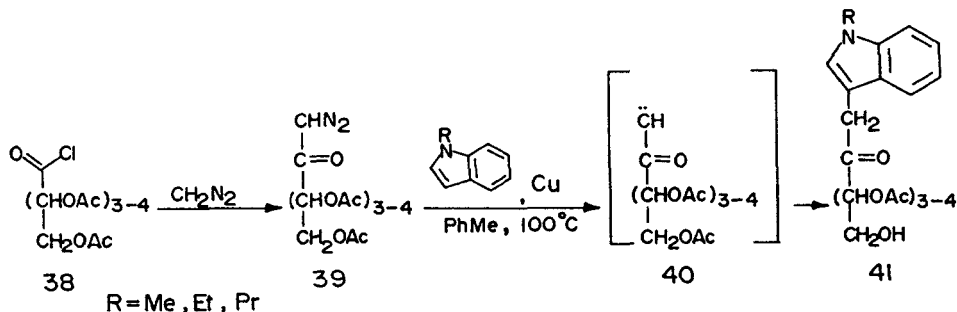
Condensation of 1-alkylamino-1-deoxy-D-fructose (**42**) with cyclohexane-1,3-diones is a simple reaction that leads to 3-(D-arabino-tetritol-1-yl)-1,5,6,7-tetrahydroindol-4-ones (**45**) in high yield [74JCS(P1)1237] (Scheme 13).

The 1,2,3,5,6,7-hexahydro-4-oxoindol-3-yl acyclo C-nucleoside **47** was formed upon catalytic reduction of the 2-hydroximinobenzofuranone derivative **46**. Chemical dehydrogenation of **47** gave the tetrahydroindol-3-yl C-nucleoside **48** [87JCS(P1)581] (Scheme 14).

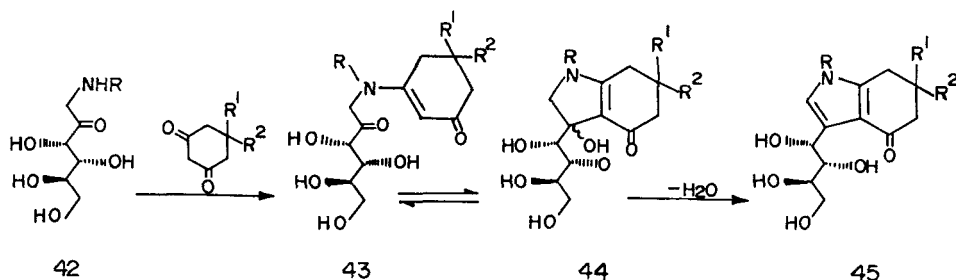
D. BENZO[c]PYRROLE C-NUCLEOSIDES

1. Phthalimid-3-yl C-Nucleosides

Diels-Alder cycloaddition of maleimide onto the furan ring of **49** gave the oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxamide **50**, which was aroma-



SCHEME 12



SCHEME 13

tized and de-*O*-benzoylated to the 3- β -D-ribofuranosylphthamide **51** [84JOC1534; 85MI9] (Scheme 15).

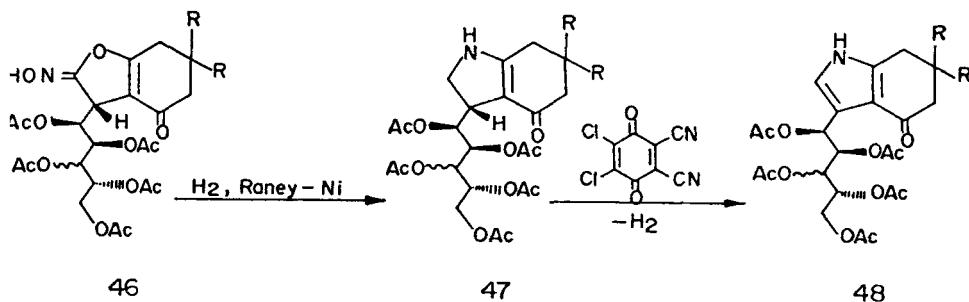
E. CARBAZOLE C-NUCLEOSIDES

1. Carbazol-1-yl C-Nucleosides

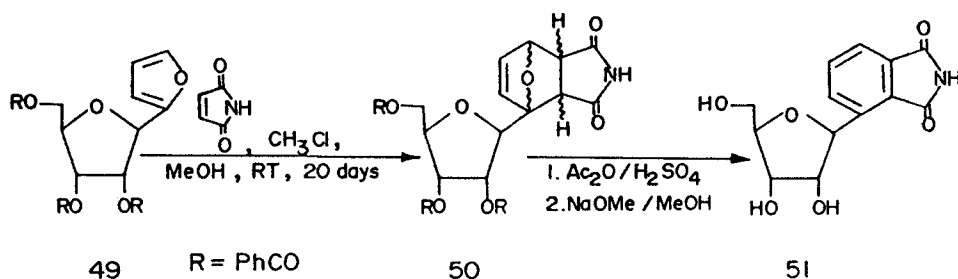
The C-nucleoside **53** was obtained by Lewis acid-catalyzed condensation of the 4- β -D-ribofuranosyl-4-oxobutanal **52** with 2,3-unsubstituted indoles [89JCS(P1)649] (Scheme 16).

2. Carbazol-4-yl C-Nucleosides

2-Allyl-1-phenylsulfonylindole reacted with the C- β -D-ribofuranosyl-nitromethane **24** in the presence of phenyl-isocyanate (see Scheme 8) to give the carbazol-4-yl C-nucleoside **54** [87JCS(CC)680] (Scheme 17).



SCHEME 14



SCHEME 15

F. PYRIDO[3,4-*b*]INDOLE *C*-NUCLEOSIDES

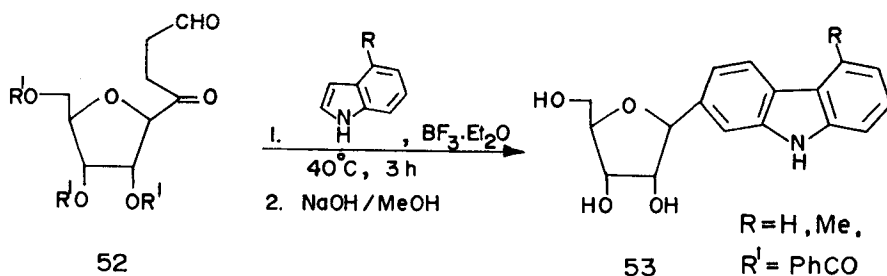
1. *Pyrido[3,4-*b*]indol-1-yl C-Nucleosides* (*β*-Carbolin-1-yl *C*-Nucleosides)

Pictet–Spengler reaction of 2,5-anhydro-D-mannose (**55**) and tryptamine hydrochloride (**56**) at ambient temperature affected the tetrahydropyridine ring formation of the (1*R*) and (1*S*)-1-(α -D-arabinofuranosyl)-1,2,3,4-tetrahydro- β -carboline **57** [83CJC2721, 83JCS(CC)601] (Scheme 18).

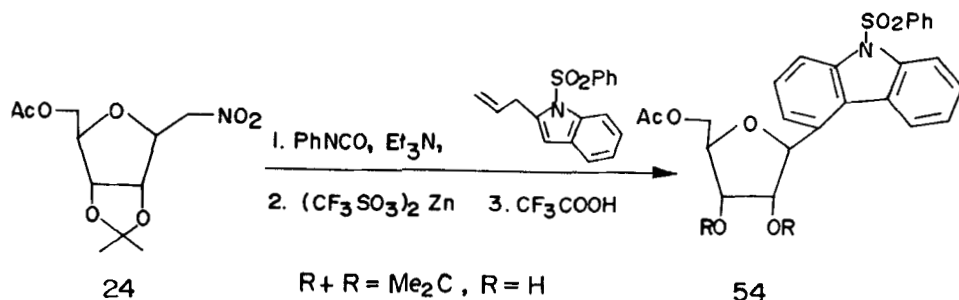
G. PYRIDO[3,4-*b*]INDOLE REVERSE *C*-NUCLEOSIDES

1. *Pyrido[3,4-*b*]indol-1-yl Reverse C-Nucleosides* (*β*-Carbolin-1-yl Reverse *C*-Nucleosides)

The reverse *C*-nucleoside **59** was prepared by cyclocondensation of tryptamine (**56**) with the protected C5 aldehyde function of **58** (95SC3027) (Scheme 19).



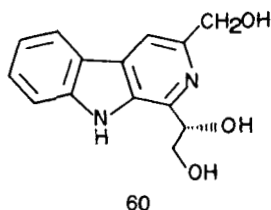
SCHEME 16



SCHEME 17

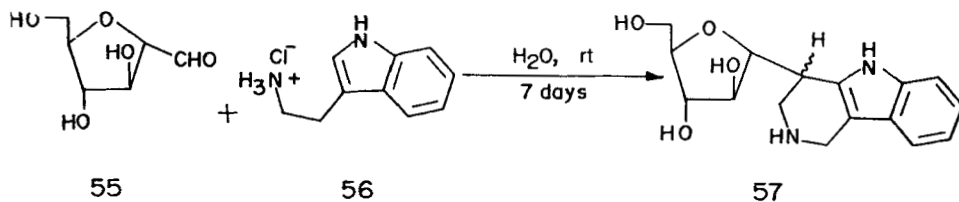
H. PYRIDO[3,4-*b*]INDOLE ACYCLO C-NUCLEOSIDES1. *The Naturally Occurring Pyrido[3,4-*b*]indol-1-yl Acyclo C-Nucleoside "Pyridindolol"*

Pyridindolol was isolated (75JAN555) from culture filtrates of *Streptomyces alboverticillatus*, and its structure was established as 1-[(1*R*)-2-dihydroxyethyl]-3-hydroxymethyl-9-*H*-pyrido[3,4-*b*]indole (**60**) (75JAN555,

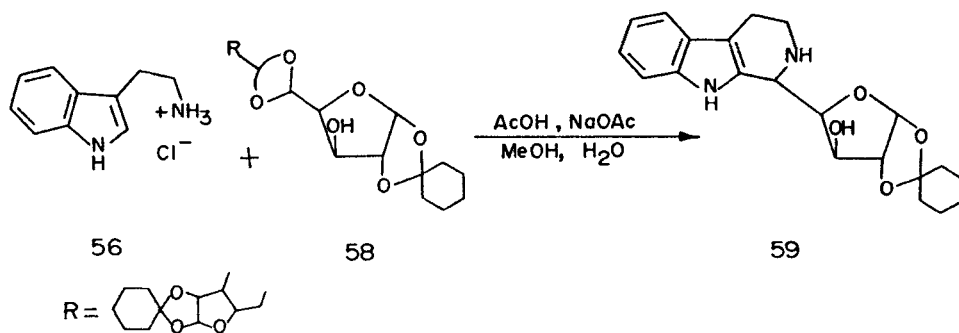


75JAN876). Pyridindolol is a specific inhibitor of neutral bovine β -galactosidase in acid media (75JAN555; 76JAN696).

(*R*, *S*) Pyridindolol (**64**) was synthesized by Pictet–Spengler reaction of tryptophan methyl ester with 2,3-*O*-isopropylidene-D-glyceraldehyde (**61**) as shown in Scheme 20 [78H(9)175; 79JOC535].



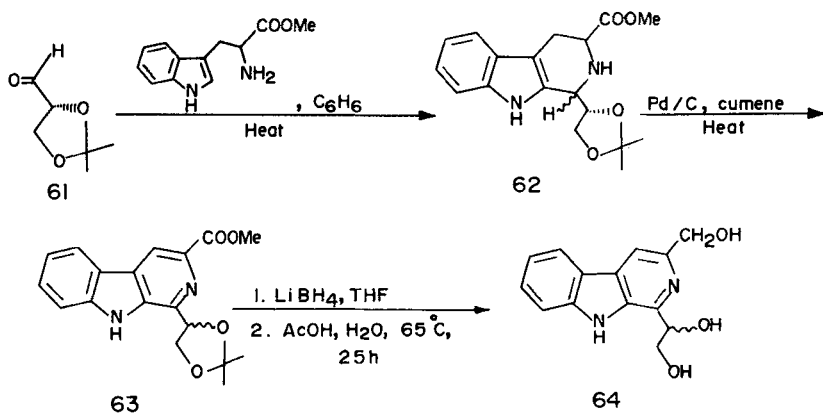
SCHEME 18



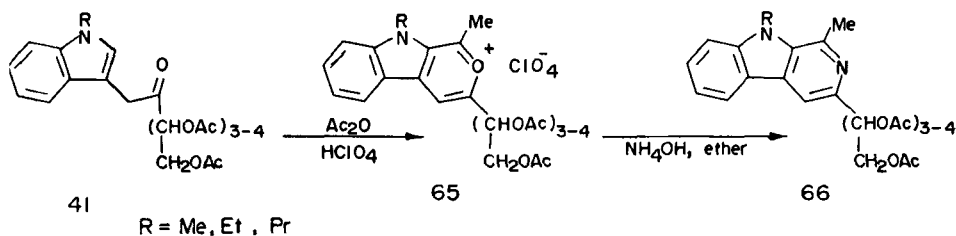
SCHEME 19

2. *Pyridol[4,3-b]indol-3-yl Acyclo C-Nucleosides (β-Carbolin-3-yl Acyclo C-Nucleosides)*

Treatment of the previously mentioned 3-(2-ulso-1-yl)indoles **41** (Section II,C,2) with acetic anhydride and perchloric acid gave the indole[2,3-*c*]pyrylium perchlorates **65**. Ammonium hydroxide in ether caused oxygen–nitrogen exchange and provided **66** [68DOK849, 68MI3] (Scheme 21).



SCHEME 20



SCHEME 21

I. 1,2,4-TRIAZOLO[4',3':2,3]1,2,4-TRIAZINO[5,6-*b*]INDOLE ACYCLO C-NUCLEOSIDES

1. 1,2,4-Triazolo[4',3':2,3]1,2,4-triazino[5,6-*b*]indol-3-yl Acyclo C-Nucleosides

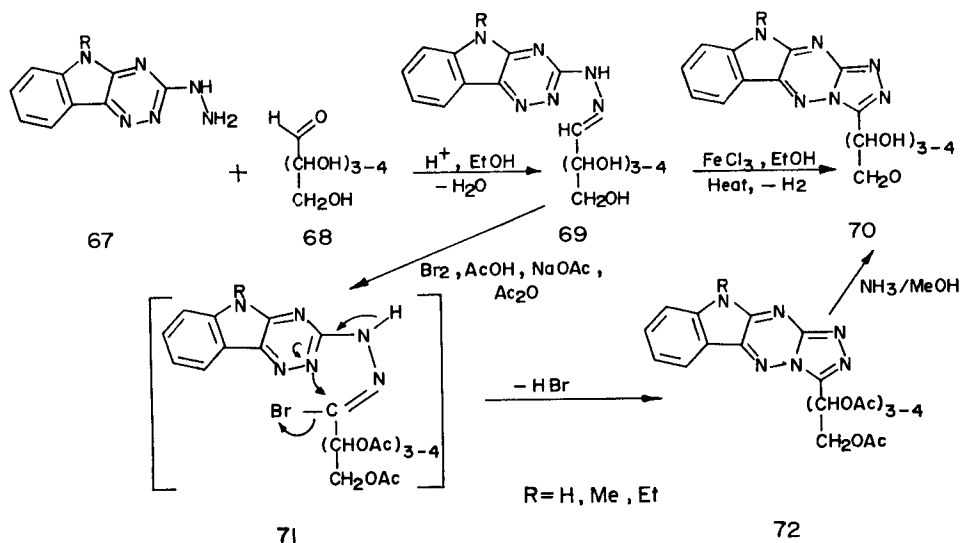
Hydrazone **69** (R = H) derived from 3-hydrazino-5*H*-1,2,4-triazino[5,6-*b*]indole (**67**, R = H) and aldose monosaccharides (**68**) produced the acyclo C-nucleoside (**70**, R = H) upon oxidative cyclization with iron(III) chloride (92BCJ546). The poly-*O*-acetyl derivatives of the 10-methyl and 10-ethyl congeners (**70**, R = Me or Et) were obtained in one step from the corresponding hydrazones (**69**, R = Me or Et) by cyclization with a mixture of bromine in acetic acid, anhydrous sodium acetate, and acetic anhydride (97UP1) (Scheme 22).

III. Condensed 1,2-Diazole C-Nucleosides

A. PYRAZOLO[1,2-*a*]PYRAZOLE ACYCLO C-NUCLEOSIDES

1. Pyrazolo[1,2-*a*]pyrazol-3-yl Acyclo C-Nucleosides

The only reported acyclo C-nucleoside of this kind **75** was prepared by Hanisch and Henseke upon heating the 1,5:4,6-dianhydro-2,3-hexodiulose bis(phenylhydrazone) **74** with copper(II) sulfate (68CB4170) (Scheme 23).

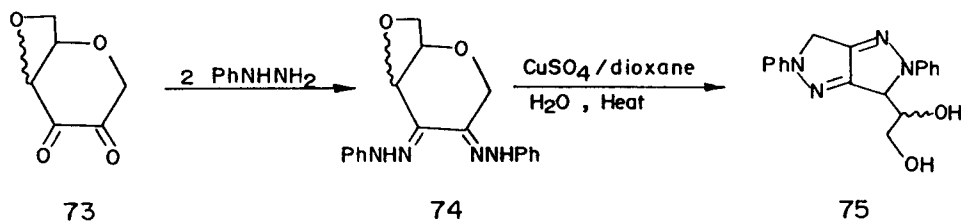


SCHEME 22

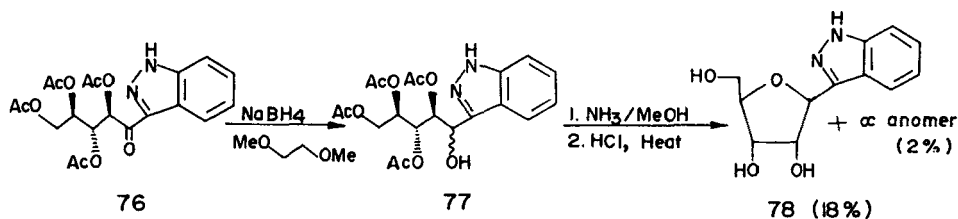
B. INDAZOLE C-NUCLEOSIDES

1. Indazol-3-yl C-Nucleosides

Dehydrocyclization of the epimeric mixture of the indazol-3-yl acyclo C-nucleoside **77** (Section III,E) by heating with hydrochloric acid afforded mainly the 3- β -D-ribofuranosylindazole **78** and its α -anomer (79JHC81) (Scheme 24).



SCHEME 23



SCHEME 24

C. INDAZOLE HOMO C-NUCLEOSIDES

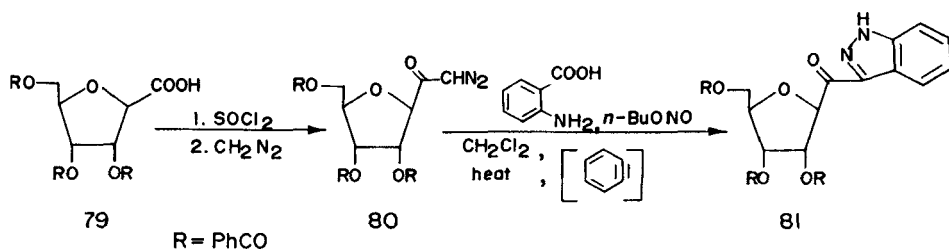
1. Indazol-3-yl Homo C-Nucleosides

The indazol-3-yl homo C-nucleoside **81** was obtained by 1,3-dipolar cycloaddition of benzyne to the 2,5-anhydro-D-allonoyldiazomethane derivative **80** (79JHC81) (Scheme 25).

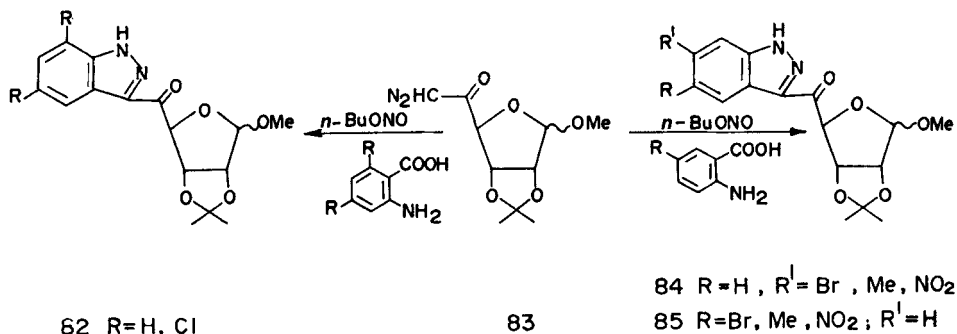
D. INDAZOLE REVERSE C-NUCLEOSIDES

1. Indazol-3-yl Reverse C-Nucleosides

Although 1,3-dipolar cycloaddition of benzyne or 4,6-dichlorobenzyne to the D-riboseuronyldiazomethane glycoside **83** afforded a single isomer (**82**) of this category of C-nucleosides, monosubstituted benzyne provided a mixture of the two isomers **84** and **85** in most cases (76JHC1241; 79JHC81) (Scheme 26).



SCHEME 25



SCHEME 26

E. INDAZOLE ACYCLO C-NUCLEOSIDES

1. Indazol-3-yl Acyclo C-Nucleosides

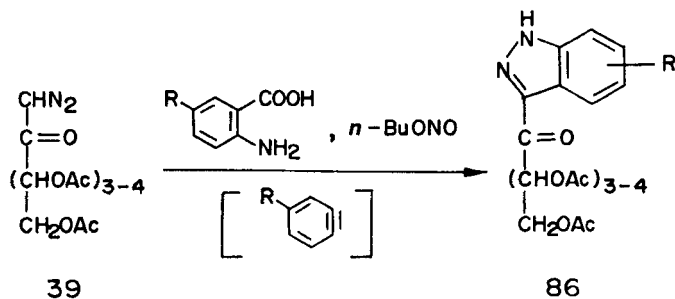
Aldonoyldiazomethane acetates **39** were used to prepare **86** by cycloaddition to arynes (76JHC1241) (Scheme 27). Acyclo C-nucleosides **86** showed a significant antitumor activity against HeLa cells (79JHC81).

IV. Condensed 1,3-Diazole C-Nucleosides

A. FURO[2,3-*d*]IMIDAZOLE ACYCLO C-NUCLEOSIDES

1. Furo[2,3-*d*]imidazol-5-yl Acyclo C-Nucleosides

The reaction product of 2-amino-2-deoxy-D-glucopyranose (**87**) with alkyl or aryl isocyanates or isothiocyanates were previously assigned the structure of 1,2-dideoxy-D-glucopyrano[1,2-*d*]imidazolidin-2-ones (**89**, Z =

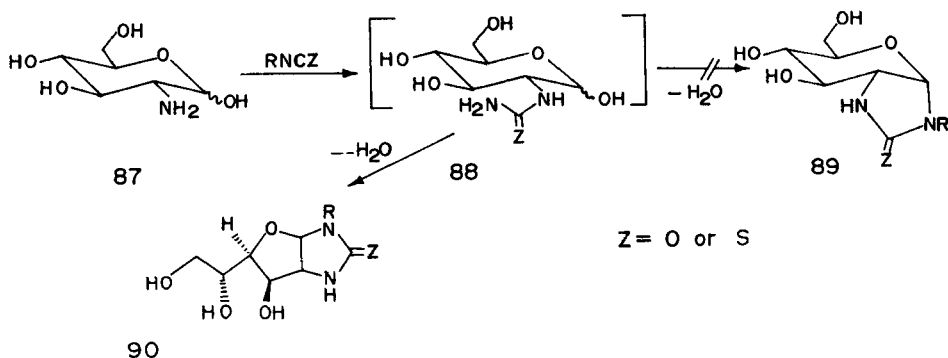


SCHEME 27

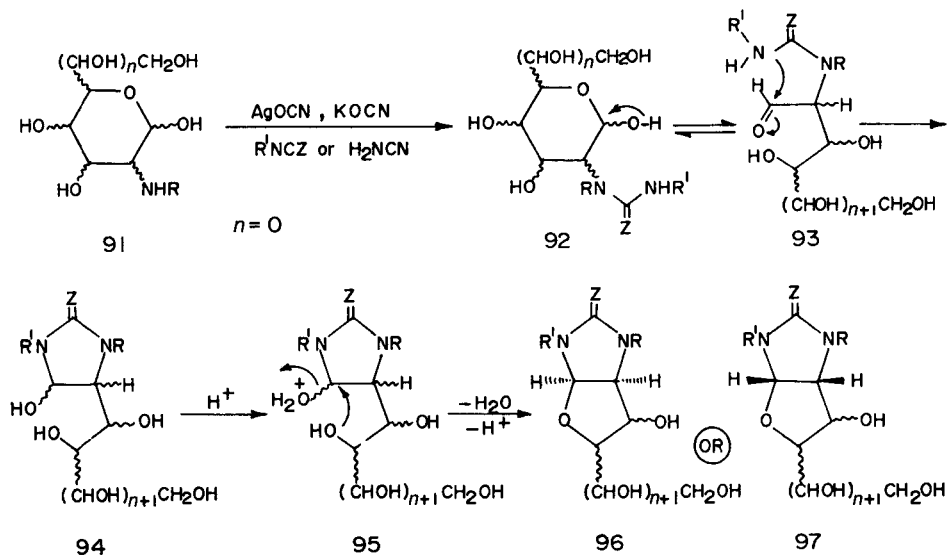
O) (56CB1246; 61HCA403; 75OPP291; 79JAN436) or the corresponding 2-thiones (**89**, $Z = S$) [61AQ(B)379; 63LA(669)146; 64AQ(B)653; 65NEP6507269, 65NEP6507271, 65NEP6507423]. Results of quantitative oxidation with sodium periodate or lead tetra-acetate [68HCA569; 74AQ(C)57], ^1H NMR [68HCA569; 84MI8; 86AQ(C)11; 91MI5], and ^{13}C NMR (91MI5) spectral data, in addition to the X-ray crystallographic analysis [74AX(B)1801; 76AX(B)1363, 76AX(B)2115, 76CSC353, 76CSC369; 78AX(B)184; 79AQ1002; 80AX(B)3048; 83AX(C)1418; 84AX(C)898; 85AX(C)277, 85AX(C)1658; 86AQ(C)11, 86AX(C)454, 86AX(C)1659; 91MI5; 93MI5; 95ZK506], however, indicated that these compounds are in fact the 1,2-dideoxy-D-glucofurano[1,2-*d*]imidazolidin-2-ones (**90**, $Z = O$) and the corresponding 2-thiones (**90**, $Z = S$). Compounds **90** were produced from the initially formed 2-deoxy-2-ureido- or 2-thioureidoglucopyranoses **88**. The structure of compounds **90** conform with their classification as acyclo C-nucleosides, namely: 1a,4a,5,6-tetrahydro-6-hydroxy-5-[(2*R*)-1,2-dihydroxyethyl]-*cis*-furo[2,3-*d*]imidazol-3-one (**90**, $Z = O$) or the corresponding 3-thioxo congeners **90** ($Z = S$) (Scheme 28).

This reaction was applied to other 2-amino- and 2-alkylamino-2-deoxyaldohexoses (**91**; $n = 0$, $R = \text{H}$, alkyl) [74AQ(C)57; 79AQ1002; 84MI7, 84MI8; 86AQ(C)11; 87MI3; 88MI6; 90MI4; 91MI5; 93T2655; 94T3273; 95ZK506], as well as 2-amino- and 2-alkylamino-2-deoxyaldohexoses (**91**; $n = 1$, $R = \text{H}$, alkyl) (87MI2; 89MI4; 93T2676), to yield **96** or **97**. Some 3-imino (90MI5) and 3-selenoxo derivatives (92MI4) of **96** or **97** were also prepared (Scheme 29).

The broad-spectrum antibiotic streptozotocin **98** is a 2-deoxy-2-ureido-D-glucopyranose derivative and, consequently, afforded the furo[2,3-*d*]imidazol-6-yl acyclo C-nucleoside **99** when treated with sulfamic acid or with hydrogen and palladium (67JA4808; 76JAN1218; 79JOC9) (Scheme 30).



SCHEME 28



$n = 0$ or 1 ; $Z = O, S, Se, NH$; $R = H, Me, Et, Pr, ArCH_2$; $R' = H, Ar$

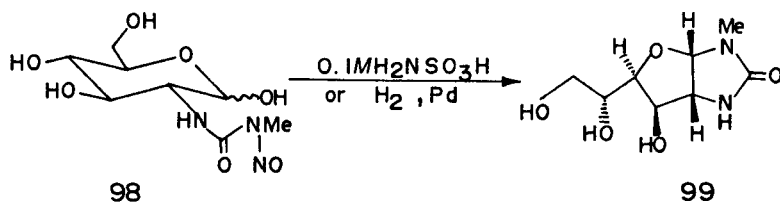
SCHEME 29

The 3-thioxo-furo[2,3-*d*]imidazol-6-yl acyclo *C*-nucleosides **101** undergo facile acid-catalyzed tetrahydrofuran ring opening to give the imidazol-4-yl acyclo *C*-nucleosides **100** (84MI11; 88MI8) and *S*-benzylation to **102** (84MI6) (Scheme 31).

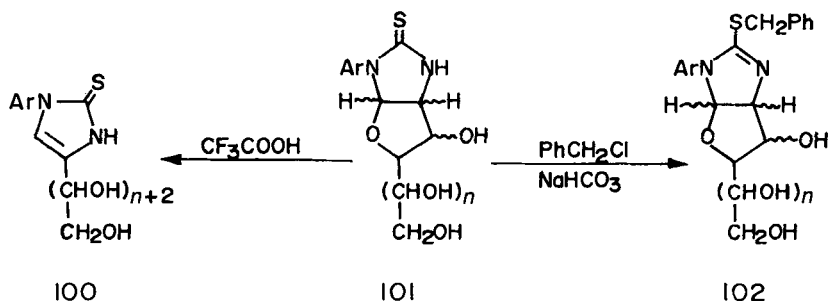
B. BENZIMIDAZOLE C-NUCLEOSIDES

1. Benzimidazol-2-yl *C*-Nucleosides

Heating 2-(*D*-tetritol-1-yl)benzimidazoles (**103**) (Section IV,C) with an acid in the presence of zinc(II) chloride caused dehydrocyclization of their



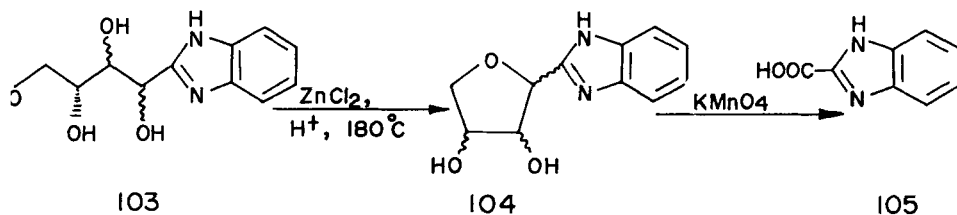
SCHEME 30



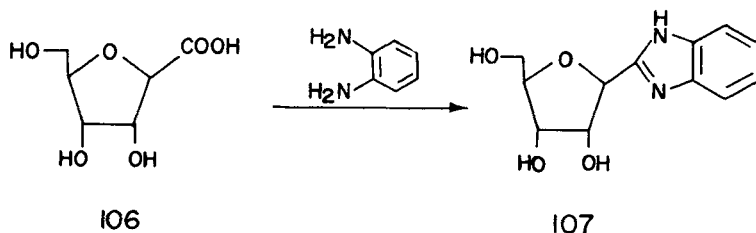
SCHEME 31

tetritol-1-yl chains to the corresponding 2-(α - or β -D-tetrafuranosyl)benzimidazoles (**104**). The structure of **104** was confirmed by oxidation to benzimidazole-2-carboxylic acid (**105**) [40JBC(133)293; 45JBC(159)503] (Scheme 32).

Benzimidazol-2-yl C-nucleosides (e.g., **107**) were also synthesized by condensation of anhydroaldonic acids such as 2,5-anhydro-D-allonic acid (**106**) with 1,2-diaminobenzene [50JBC(186)387; 69CCC247; 80JCS(P1)2683; 86SC35] (Scheme 33).



SCHEME 32



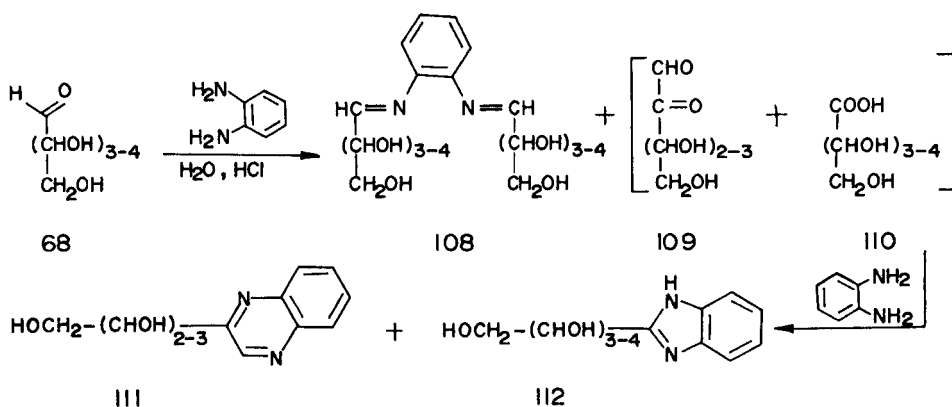
SCHEME 33

C. BENZIMIDAZOLE ACYCLO C-NUCLEOSIDES

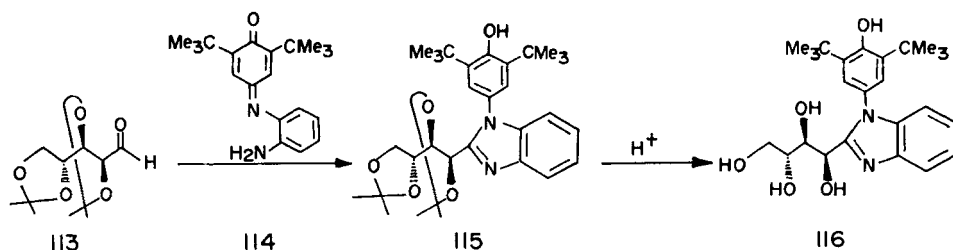
1. *Benzimidazol-2-yl Acyclo C-Nucleosides*

Condensation of 1,2-diaminobenzene with aldoses (**68**) in the presence of acids led to the formation of three products: 1,2-bis(alditol-1-ylidene-amino)benzenes (**108**), 2-(alditol-1-yl)quinoxalines (**111**) (Section XII,G), and 2-(alditol-1-yl)benzimidazoles (**112**); the yield of the latter was marginal. Formation of **111** and **112** was rationalized in terms of oxidation of the aldoses (**68**) to aldosesuloses (**109**) and aldonic acids (**110**) that cyclocondense with 1,2-diaminobenzene to give **111** and **112**, respectively (1887CB281, 1887CB2205, 1887CB3111; 1893CB3092; 01CB902; 34CB155, 34CB898, 34JA1248). This rationale was verified when the yield of benzimidazoles **112** was made to considerably increase by carrying out the reaction in the presence of copper(II) acetate as an oxidizing agent (40JOC637; 57JCS3961) or by employing aldonic acids or their lactones in place of the parent aldoses [39JA1266; 40JBC(133)293, 40NAT(L)559; 42JA1609; 43JA994, 43JA1854, 43JBC(150)345; 44JA1912, 44JCS339; 45JBC(159)503; 50JA3882; 51JA855, 51JA4907; 52JA4521; 53JA4320; 56JA4491; 65JOC79; 82MI8] (Scheme 34). The benzimidazole structure of **112** was conclusively proved by oxidation to benzimidazole-2-carboxylic acid (01CB902; 34CB898).

The plant-growth-regulating benzimidazol-2-yl acyclo C-nucleoside **116** was prepared (93ZOR1643) by cyclocondensation of the *aldehydo-D*-arabinose derivative **113** and the quinonimine **114** (Scheme 35).



SCHEME 34

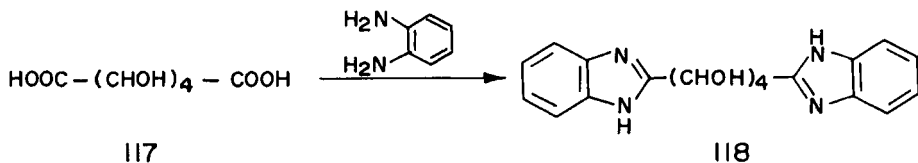


SCHEME 35

The double-headed bis(benzimidazol-2-yl) acyclo C-nucleosides **118** were obtained from the reaction of 1,2-diaminobenzene with aldaric acids of various configurations (**117**) [29JA2225; 42JBC(143)551; 48BJ(42)2, 50BJ(47)1; 73MI2] (Scheme 36).

2-(Alditol-1-yl)benzimidazoles are far superior as derivatives for characterization of aldoses to hydrazones and osazones (51MI1; 58UK179; 70CRV389, 70MI1). They have been used to characterize sugars from *Helix pomatia* (41JCS125) and nucleic acids (43JCS625; 47JCS21). With racemic tartaric acid, they form diastereoisomeric salts that are resolvable to afford the two individual enantiomers of the acid [39JA1266; 48USP2456752; 57NAT(L)367]. 5-Methyl-2-(L-arabino-tetritol-1-yl)benzimidazole showed antitumor activity against 6C3H-ED lymphosarcoma in mice (56JA4491).

Some empirical rules were devised to correlate the configuration at C1 of the alditolyl chains (C2 of the parent sugar) of 2-(alditol-1-yl)benzimidazoles with their polarimetric (42JA1612) and spectropolarimetric properties (67JA4129). The mass spectra of these compounds have been investigated (82MI8).



SCHEME 36

V. Condensed Oxazole C-Nucleosides

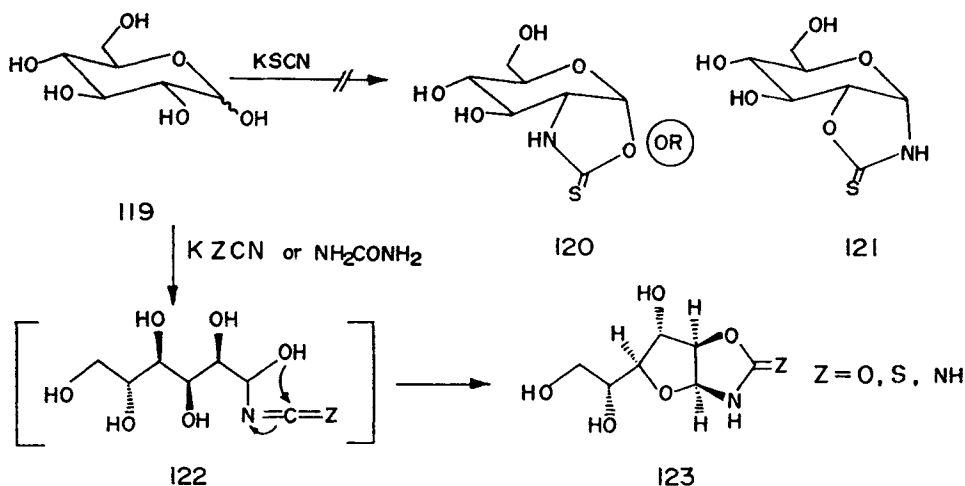
A. Furo[2,3-*d*]OXAZOLE ACYCLO C-NUCLEOSIDES

1. Furo[2,3-*d*]oxazol-5-yl Acyclo C-Nucleosides

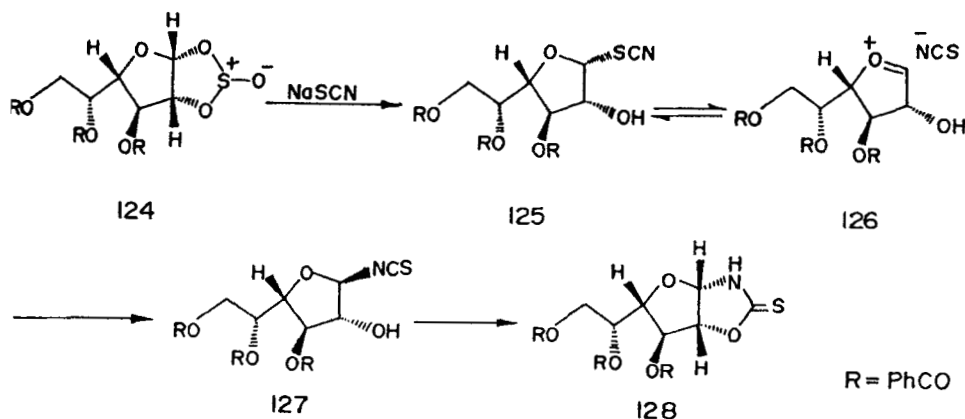
D-Glucose (**119**) reacted with potassium thiocyanate to give a product that was erroneously called the glucopyrano[3,2-*d*]oxazole (**120**) (36CB748; 45JOC267) or the glucopyrano[2,3-*d*]oxazole (**121**) [38CB590; 52CI(L)-1034] structures. Quantitative oxidation with sodium periodate (54JCS2645), acid strength measurements (59ACSA1129), ^1H NMR (68BCJ261), and ^{13}C NMR (91MI6) spectrometry, however, indicated that the product is actually the furo[2,3-*d*]oxazolidin-5-yl acyclo C-nucleoside **123** ($\text{Z} = \text{S}$). This reaction was also applied to other aldohexoses (67CB845; 94MI7). Potassium cyanate (54JCS2645; 91MI6; 94MI7; 95MI1; 96AJC409) and urea (89MI6; 91MI8) also reacted with aldoses to give the corresponding **123** ($\text{Z} = \text{O}$ or NH) (Scheme 37).

The 3,5,6-tri-*O*-benzoyl derivative **128** of **123** ($\text{R} = \text{PhCO}$) has been prepared by treating the 1,2-*O*-sulfinyl- α -D-glucopyranose derivative **124** with sodium thiocyanate (95TL5347) (Scheme 38).

1-Phenylfuro[2,3-*d*]oxazolidin-5-yl acyclo C-nucleoside **130** was obtained by cyclization of either of the 1-[2-*O*-(1-phenylcarbamoyl)-D-glucopyranosyl]piperidine **129** (69JOC2654) or methyl 2-*O*-(phenylcarbamoyl)- α -D-glucopyranoside (**131**) [74ACSA(B)559] (Scheme 39).



SCHEME 37



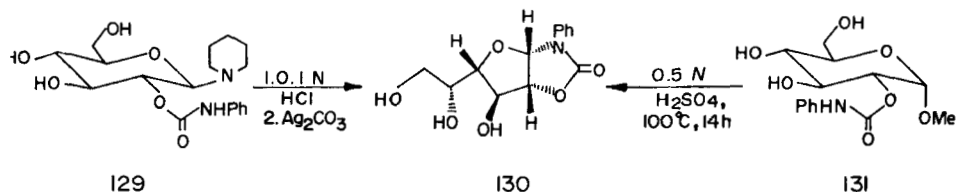
SCHEME 38

B. FURO[3,2-*d*]OXAZOLE ACYCLO C-NUCLEOSIDES

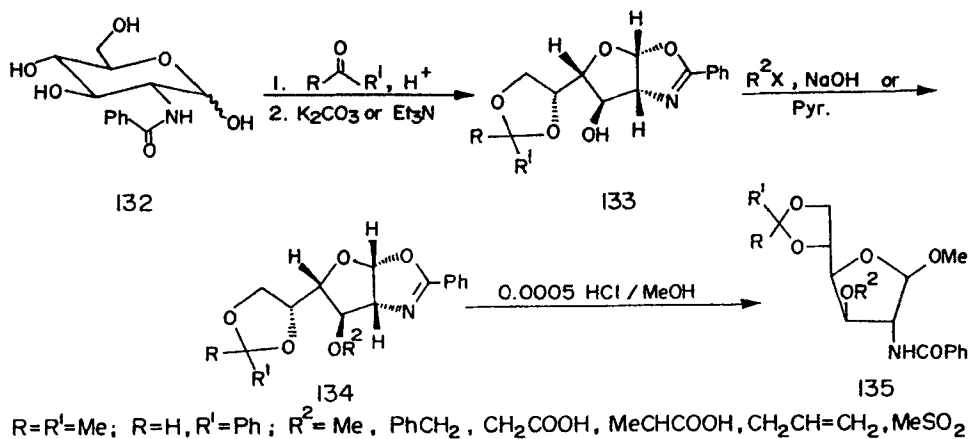
1. Furo[3,2-*d*]oxazol-5-yl Acyclo C-Nucleosides

Ketalization (59CB1288; 64ACSA185) or acetalation (68IZV2655) of 2-benzamido-2-deoxy-D-glucose **132** took place with simultaneous sugar ring contraction and oxazoline ring formation; the product is the tetrahydrofuro[3,2-*d*]oxazolin-5-yl acyclo C-nucleoside **133** having the fused rings of the heterocyclic system *cis*-fused. The oxazoline ring of **133** is stable to bases so that its C5 OH can be etherified [61NAT(L)495; 68JCS(C)1903] or esterified (62CB996) in basic media to the corresponding derivatives **134**. However, the oxazoline ring of **134** is even more sensitive to acids than are dioxolane rings; they undergo β -glycosidation with alcohols in the presence of very dilute acids to **135** [63CB2019; 68JCS(C)1903] (Scheme 40).

Treatment with sodium hydroxide caused evolution of diazomethane from the antibiotic streptozotocin (**98**) and formation of the 3a,5,6,6a-tetrahydro-6-hydroxy-5-[(2*R*)-1,2-dihydroxy-ethyl]-*cis*-furo[2,3-*d*]oxazol-2-one **136** (79JOC9) (Scheme 41).



SCHEME 39



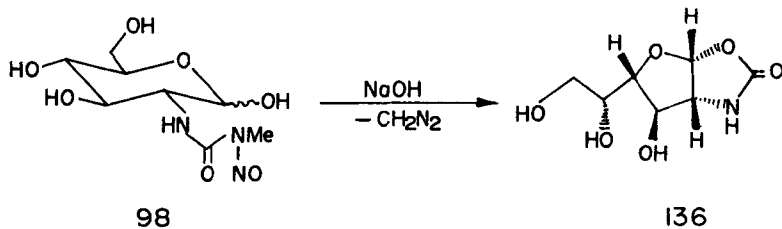
SCHEME 40

The 6-deoxy-L-congener **141** of **136** was obtained from 2-amino-2-deoxy-L-glucopyranose **137** as shown in Scheme 42 (76BCJ313).

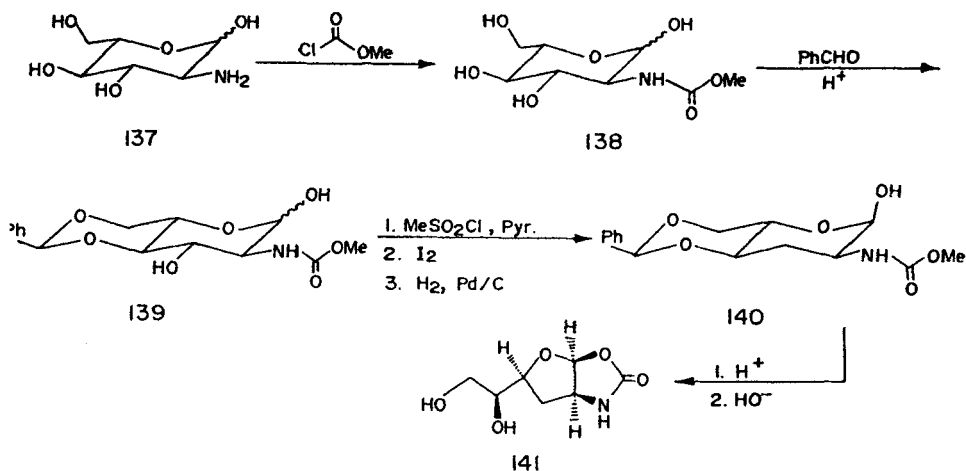
C. Furo[3,4-*d*]oxazole Acyclo C-NUCLEOSIDES

1. Furo[3,4-*d*]oxazol-6-yl Acyclo C-Nucleosides

Gigg and Warren cyclized the methyl 2-benzamido-2-deoxy-5,6-*O*-isopropylidene-4-*O*-methylsulfonyl- β -D-glucopyranoside **135** to the furo[3,4-*d*]oxazin-6-yl acyclo C-nucleoside **142** by treatment with sodium methoxide in methanol [65JCS1351, 65TL1303; 66JCS(C)1872] (Scheme 43).



SCHEME 41



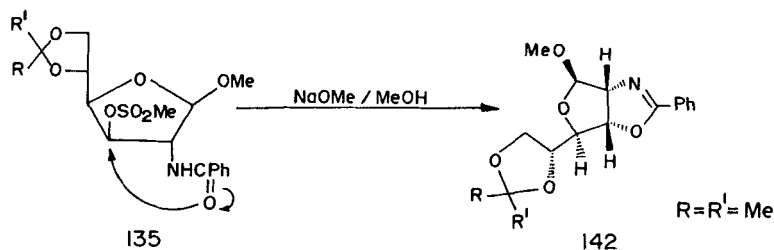
SCHEME 42

D. THIAZOLO[3,4-*c*]OXAZOLE ACYCLO C-NUCLEOSIDES1. *Thiazolo[3,4-*c*]oxazol-7-yl Acyclo C-Nucleosides*

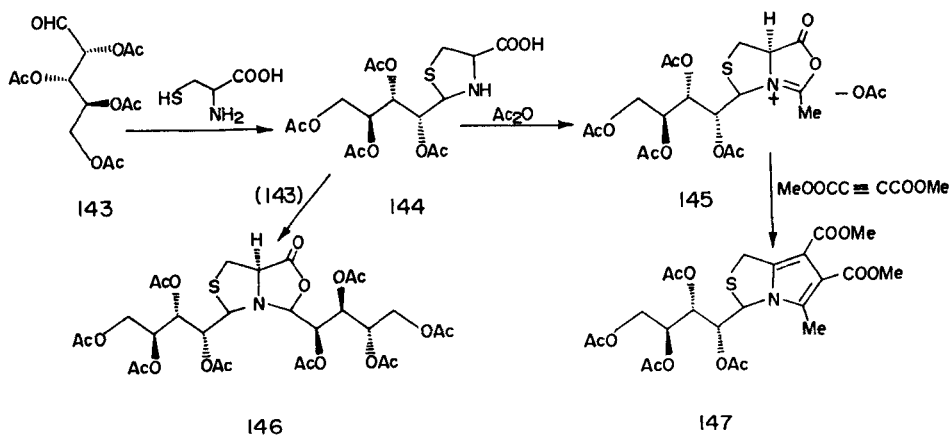
Cylocondensation of tetra-*O*-acetyl-aldehydo-L-arabinose (**143**) with L-cysteine gave the thiazol-2-yl C-nucleoside **144** (76LA450). Acetylation of the latter gave the 7-(tetra-*O*-acetyl-D-arabino-tetritol-1-yl)thiazolo[3,4-*c*]oxazole **145** (94M189) (Scheme 44).

2. *Thiazolo[3,4-*c*]oxazoldi-1,7-yl Acyclo C-Nucleosides*

Treatment of the thiazol-2-yl acyclo C-nucleoside **144** with an additional molecule of **137** affected oxazole ring closure of the thiazolo[3,4-*c*]oxazole acyclo C-nucleoside **146** having two alditolyl chains (76LA450) (Scheme 44).



SCHEME 43



SCHEME 44

E. BENZOXAZOLE C-NUCLEOSIDES

1. Benzoxazol-2-yl C-Nucleosides

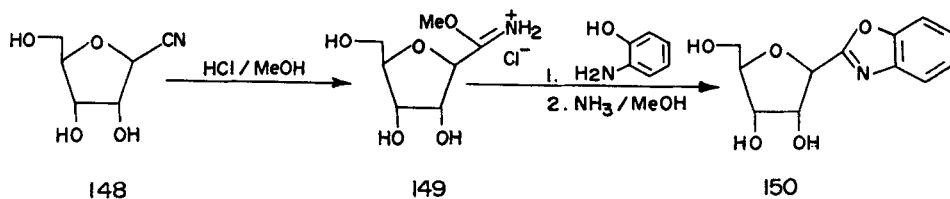
The 2- β -D-ribofuranosylbenzoxazole **150** was formed upon reacting β -D-ribofuranosylformimide (**148**) with 2-aminophenol (86MI4) (Scheme 45).

VI. Condensed Thiazole C-Nucleosides

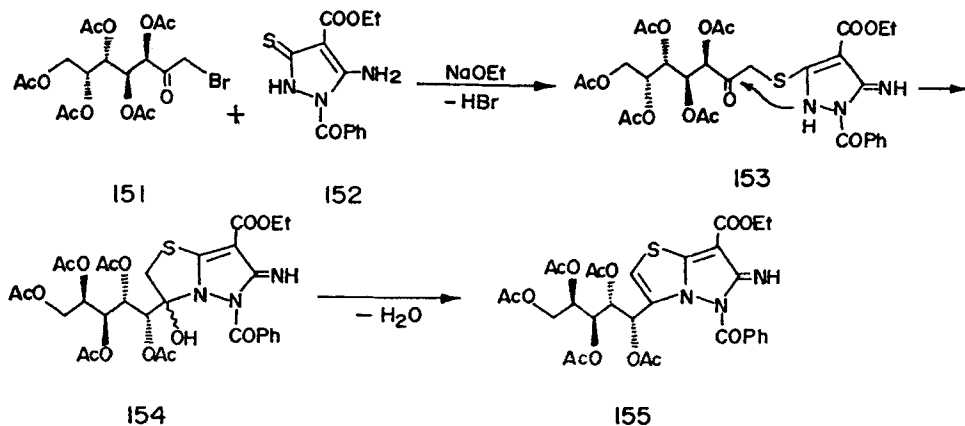
A. PYRROLO[1,2-*c*]THIAZOLE ACYCLO C-NUCLEOSIDES

1. Pyrrolo[1,2-*c*]thiazol-7-yl Acyclo C-Nucleosides

Synthesis of the acyclo C-nucleoside **147** was achieved by [3+2] cycloaddition of thiazolo[3,4-*c*]oxazole C-nucleoside **145** onto dimethylacetylene dicarboxylate (94M189) (Scheme 44).



SCHEME 45



SCHEME 46

B. PYRAZOLO[5,1-*b*]THIAZOLE ACYCLO C-NUCLEOSIDES

1. *Pyrazolo*[5,1-*b*]thiazol-3-yl Acyclo C-Nucleosides

Reaction of 1-bromo-1-deoxy-D-*galacto*-heptulose (**151**) with the pyrazole derivative **152** in the presence of sodium methoxide gave the C-nucleoside **155** (86PHA548) (Scheme 46).

C. IMIDAZO[2,1-*b*]THIAZOLE ACYCLO C-NUCLEOSIDES

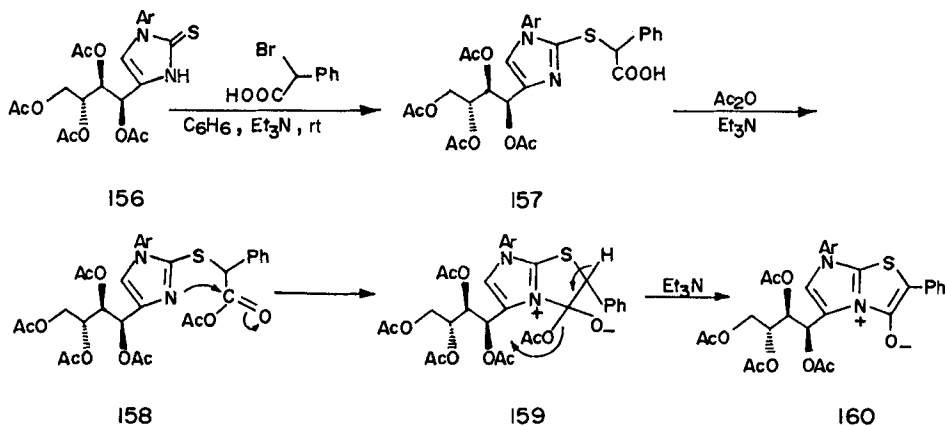
1. *Imidazo*[2,1-*b*]thiazol-5-yl Acyclo C-Nucleosides

The thiazole ring of the 5-(D-*arabino*-tetritol-1-yl)-imidazo[2,1-*b*]thiazolium olate **160** was assembled onto the imidazole ring of 4-(tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)imidazoline-2-thione (**156**) by reaction with 2-bromophenylacetic acid (91MI7) (Scheme 47).

D. FURO[2',3':4,5]IMIDAZO[2,1-*b*]THIAZOLE ACYCLO C-NUCLEOSIDES

1. *Furo*[2',3':4,5]imidazo[2,1-*b*]thiazol-6-yl Acyclo C-Nucleosides

2-Thioxo-furo[2,3-*d*]imidazolidin-6-yl acyclo C-nucleoside acetate **161** condensed with 2-bromophenylacetic acid to form **162**, which cyclized by



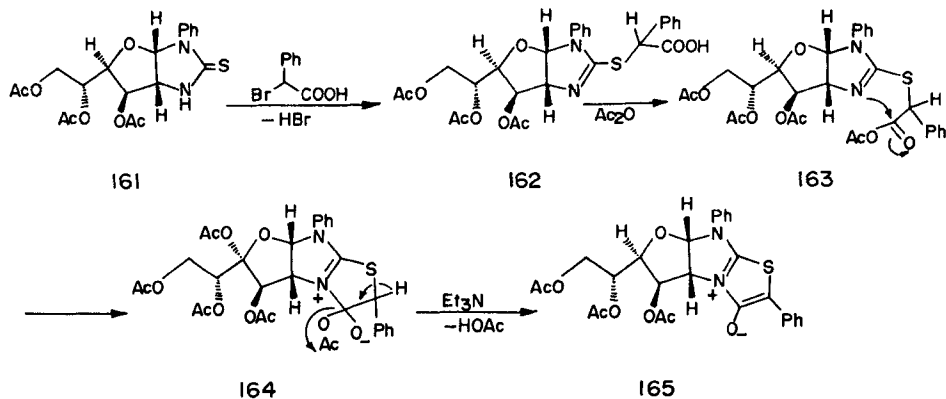
SCHEME 47

heating and acetic anhydride and subsequent treatment with triethylamine to furo[2',3:4,5]imidazo[2,1-*b*]thiazolium-3-olate acyclo *C*-nucleoside acetate **165** (91MI7) (Scheme 48).

E. BENZOTHAIAZOLE *C*-NUCLEOSIDES

1. Benzothiazol-2-yl *C*-Nucleosides

O-Protected glycofuranosyl cyanides (e.g., **166**) [78KGS893; 81ACH (106)61; 82ACH(109)229] and glycopyranosyl cyanides (77MI6; 94MI5) reacted with 2-aminothiophenol to furnish the corresponding benzothiazol-

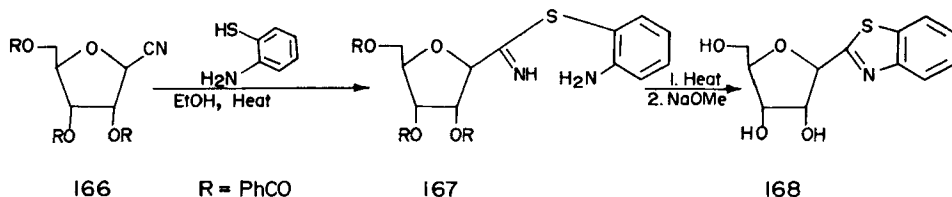


SCHEME 48

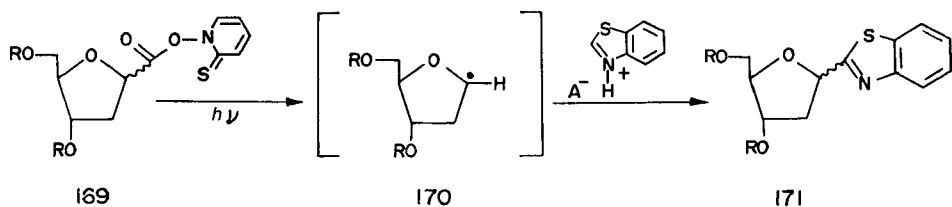
2-yl C-nucleoside (e.g., **168**). The reaction takes place, most probably, through the intermediate thioimide **167** (Scheme 49).

Benzothiazol-2-yl C-nucleosides were also obtained by a different mode of synthesis that involved the free radical coupling of the sugar subunit with the heterocycle residue. The 2-deoxy-D-ribofuranosyl free radical **170**, formed by photolysis of the 2-thiopyridone-*N*-(2,5-anhydro-3-deoxy)-D-allonoate **169**, reacted with benzothiazolium camphorsulfonate to form a mixture of 2-(α and β -2-deoxy-D-ribofuranosyl) benzothiazoles **171** (92CL1673) (Scheme 50).

Coupling free radical **173**, obtained by decarboxylative photolysis of the acid **172** in the presence of diacetoxyiodobenzene (DAIB), with benzothiazolium trifluoroacetate, gave **174**. Unlike the previous synthesis, this coupling ensued diastereoselectively as a result of the nonplanarity of the free radical centered on the carbon at the junction of the two rings (92TL7575) (Scheme 51).



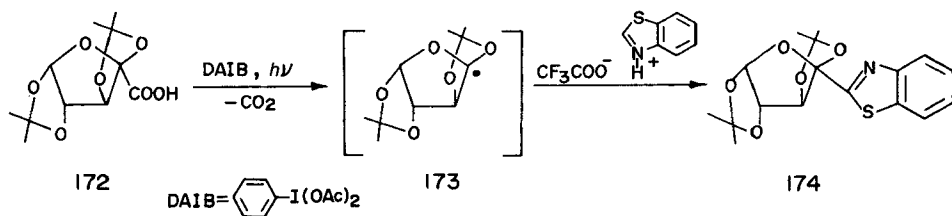
SCHEME 49



AH = Camphorsulfonic acid

R = PhCO

SCHEME 50



SCHEME 51

F. BENZOTHAIAZOLE CARBOCYCLIC C-NUCLEOSIDES

1. *Benzothiazol-2-yl Carbocyclic C-Nucleosides*

The carbocyclic C-nucleoside analog **177** pertaining to this class was prepared by coupling free radical **176** with benzothiazolium trifluoroacetate [94JCS(P1)2407] (Scheme 52) in a similar way to that used for the preparation of **171**.

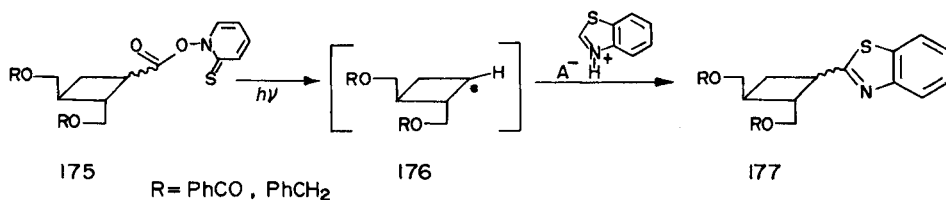
G. BENZOTHAIAZOLE ACYCLO C-NUCLEOSIDES

1. *Benzothiazol-2-yl Acyclo C-Nucleosides*

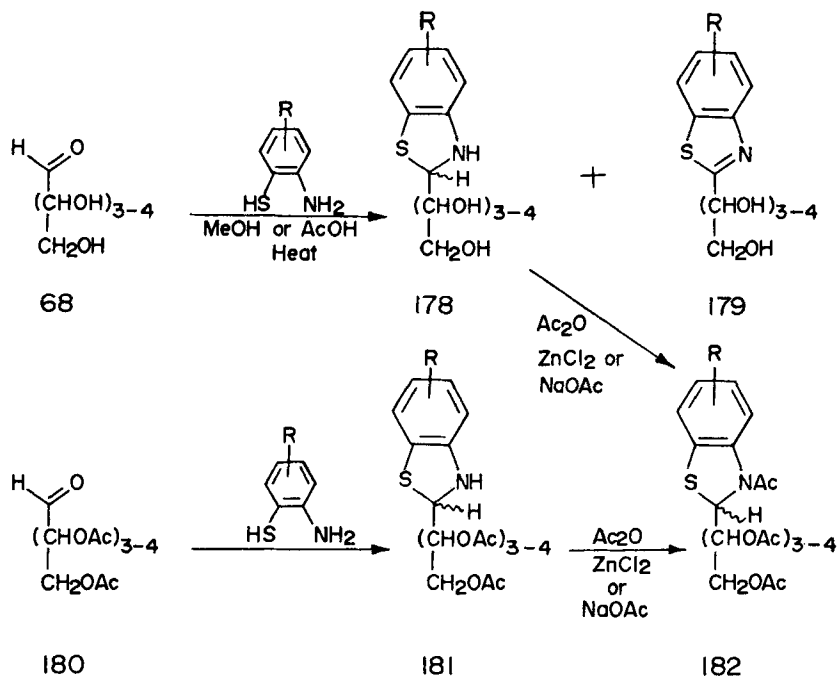
Aldose monosaccharides (**68**), when condensed with 2-aminothiophenols, gave the 2-(alditol-1-yl)benzothiazolines (**178**) [51JA5908; 69ACH(62)65; 70MI5; 74MI9; 77MI1]. In one case (77MI5), this reaction was reported to yield a mixture of the benzothiazol-2-yl (**179**) and benzothiazolin-2-yl (**178**) C-nucleosides. Acetylation of **178** affected both *N*- and *O*-acetylation to give **182**, which were also obtained by condensation of 2-aminothiophenol with poly-*O*-acetyl-*aldehydo*-sugars (**180**) followed by *N*-acetylation [69ACH(62)65; 70MI5] (Scheme 53).

Poly-*O*-acetyl-benzothiazol-2-yl acyclo C-nucleosides **184** were prepared in good yields from the aldononitrile acetates (**183**) [69ACH(62)179; 82ACH(109)229] or aldonyl chloride acetates **38** [69ACH(62)179] by reaction with 2-aminothiophenols (Scheme 54).

Synthesis by carbon-carbon bond formation between an acyclic sugar derivative and the benzothiazole ring system has also been utilized for the synthesis of these C-nucleosides. In one report, 2,3-*O*-isopropylidene-D-glyceraldehyde (**61**) was coupled with 2-trimethylsilylbenzothiazole to afford the *N*-nucleoside **185** as an intermediate, which underwent a 1,2-shift of the alditolyl chain to produce the C-nucleoside **186** (85TL5477) (Scheme 55).

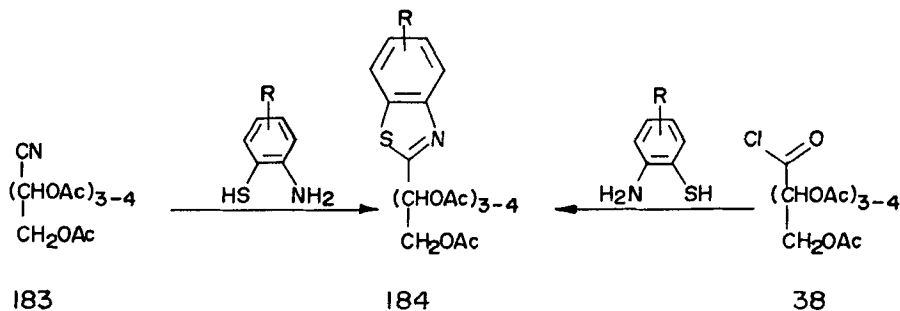


SCHEME 52

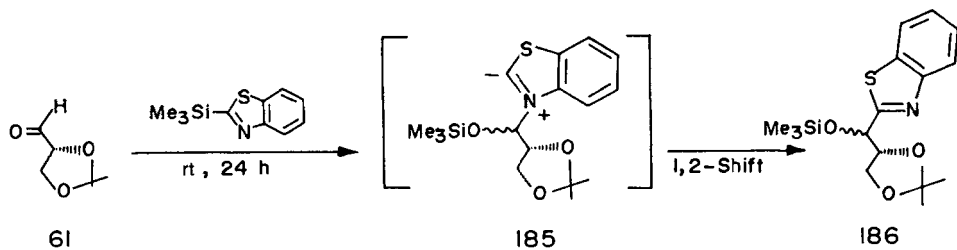


SCHEME 53

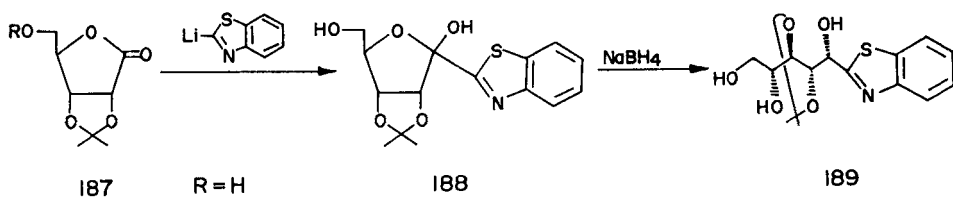
According to other reports (73DOK99; 74JOC1374), C—C bond formation was achieved by reacting 2-benzothiazolyl lithium with *O*-protected aldonolactones such as **187** to form the hemiacetal (lactol) type of C-nucleosides **188**, which were reduced with sodium borohydride to **189** (Scheme 56).



SCHEME 54



SCHEME 55



SCHEME 56

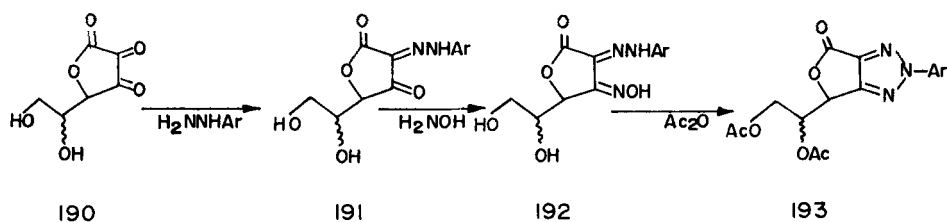
The relation between CD spectral characteristics and configuration of the alditolyl chains of benzothiazol-2-yl *C*-nucleosides (72T4197) and their *O*-acetyl derivatives (73MI1) was studied.

VII. Condensed 1,2,3-Triazole *C*-Nucleosides

A. Furo[3,4-*d*]1,2,3-TRIAZOLE ACYCLO *C*-NUCLEOSIDES

1. Furo[3,4-*d*]1,2,3-triazol-4-yl Acyclo *C*-Nucleosides

Oximation of dehydro-D- or L-ascorbic acid 2-arylhydrazones **191** followed by dehydrative cyclization and concomitant *O*-acetylation of the resulting 2-arylhydrazones-3-oximes **192** led to the formation of the 1,2,3-



SCHEME 57

triazole ring of the furo[3,4-*d*]1,2,3-triazol-4-yl acyclo C-nucleosides **193** (77MI7; 79MI8; 82MI7; 83MI10; 88MI1; 93MI1) (Scheme 57).

VIII. Condensed 1,3,4-Thiadiazole C-Nucleosides

A. 1,2,4-TRIAZOLO[3,4-*b*]1,3,4-THIADIAZOLE ACYCLO C-NUCLEOSIDES

1. 1,2,4-Triazolo[3,4-*b*]1,3,4-thiadiazol-6-yl Acyclo C-Nucleosides

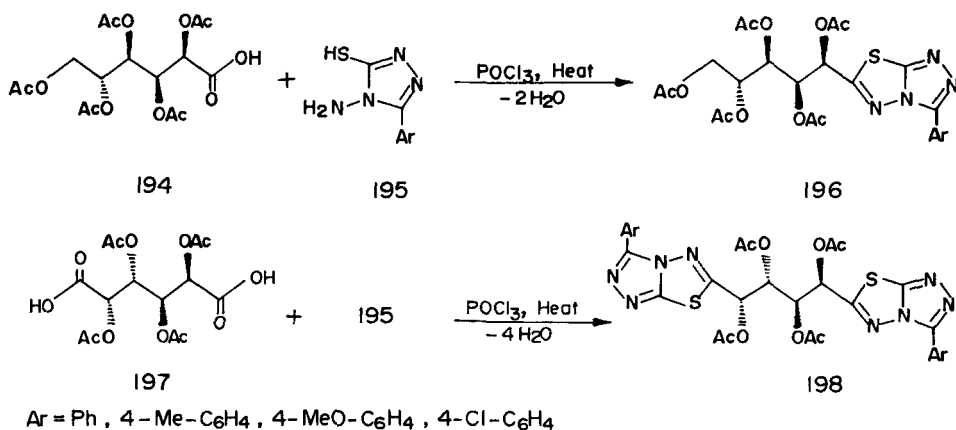
The only known examples of this sort are **196** and **198**, and they were synthesized by cyclocondensation of 4-amino-3-aryl-1,2,4-triazole-5-thiols (**195**) with poly-*O*-acetyl derivatives of aldonic (**194**) or aldaric acids (**197**), respectively, in the presence of phosphoryl chloride (95PHA534) (Scheme 58).

IX. Condensed Azine C-Nucleosides

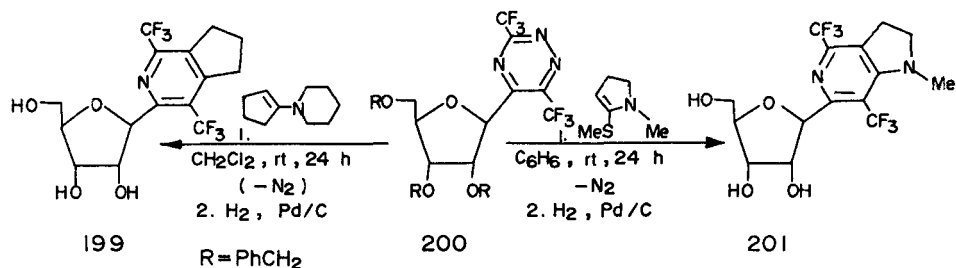
A. CYCLOPENTA[*c*]PYRIDINE C-NUCLEOSIDES

1. Cyclopenta[*c*]pyridin-3-yl C-Nucleosides

Inverse [4+2]cycloaddition of the activated 1,2,4-triazin-4-yl C-nucleoside **200** with the electron-rich 1-pyrrolidinocyclopentene and subsequent elimination of a nitrogen molecule led to the formation of the cyclopenta[*c*]pyridin-3-yl C-nucleoside **199** (95AP175) (Scheme 59).



SCHEME 58



SCHEME 59

B. PYRROLO[2,3-*b*]PYRIDINE C-NUCLEOSIDES

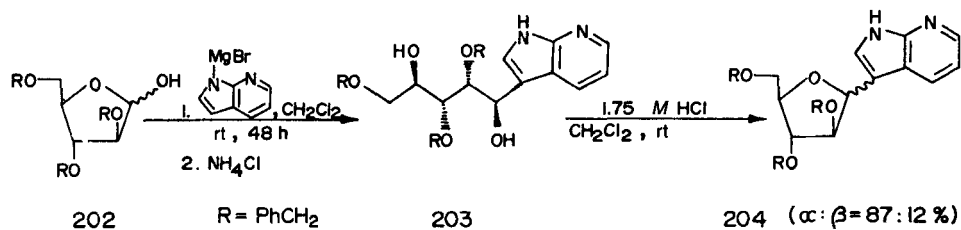
1. Pyrrolo[2,3-*b*]pyridin-3-yl C-Nucleosides

The reaction medium was found to be crucial in determining whether *N*- or *C*-alkylation of 1-pyrrolo[2,3-*b*]pyridine magnesium bromide with *aldehydo*-sugar derivatives, such as 2,3,5-tri-*O*-benzyl-D-arabinofuranose **202**, will take place. Although predominant *N*-alkylation occurred in THF, *C*-alkylation at C3 of the pyrrolo[2,3-*b*]pyridine system became almost exclusive in dichloromethane to give the 3-(D-*manno*-tetritol-1-yl)pyrrolo[2,3-*b*]pyridine **203** as a single enantiomerically pure isomer as ascertained by ^1H NMR, ^{13}C NMR, and reversed-phase HPLC. Acid-catalyzed dehydrocyclization of **203** gave a mixture of the two anomers of **204** (91JOC5466) (Scheme 60).

C. PYRROLO[3,2-*c*]PYRIDINE C-NUCLEOSIDES

1. Pyrrolo[3,2-*c*]pyridin-6-yl C-Nucleosides

Utilization of 1-methyl-2-methylthio-2-pyrroline as a dienophile to react with **200** produced the 1-methyl-6-(β -D-ribofuranosyl)pyrrolidino[3,2-*c*]pyridine **201** (95AP175) (Scheme 59).



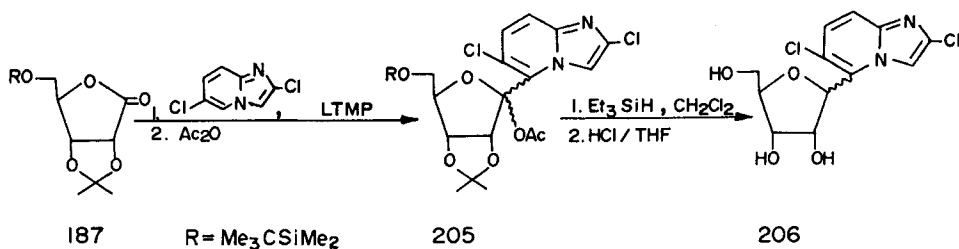
SCHEME 60

D. IMIDAZO[1,2-*a*]PYRIDINE C-NUCLEOSIDES1. *Imidazo[1,2-*a*]pyridin-5-yl C-Nucleosides*

Ribosylation of lithiated 2,6-dichloroimidazo[1,2-*a*]pyridine with the D-ribo-1,4-lactone derivative **187** occurred, unexpectedly, at C5 instead of C3 to afford the hemiacetal C-nucleoside **205**. Compound **205** was *O*-acetylated and reductively deacetoxyated with triethylsilane in the presence of a Lewis acid to the anomeric mixture of **206**. The $\alpha:\beta$ ratio of **206** depended on the Lewis acid (96TL2365) (Scheme 61).

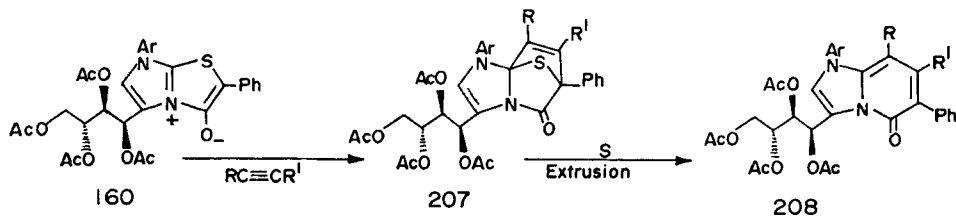
E. IMIDAZO[1,2-*a*]PYRIDINE ACYCLO C-NUCLEOSIDES1. *Imidazo[1,2-*a*]pyridin-3-yl Acyclo C-Nucleosides*

Imidazo[2,1-*b*]thiazolium-3-olate **160** (Section VI,C; Scheme 47) underwent rapid cycloaddition with acetylene mono- and dicarboxylic esters to give the imidazo[1,2-*a*]pyridin-3-yl acyclo C-nucleoside **208** through sulfur extrusion from the intermediate **207** (91MI7) (Scheme 62).



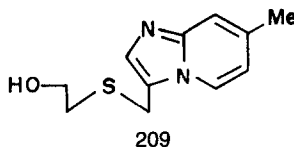
LTMP = Lithiated tetramethylpiperidine

SCHEME 61



Ar = 4-EtO-C₆H₄ ; R = R' = COOMe ; R or R' = H or COOMe

SCHEME 62



The imidazo[1,2-*a*]pyrid-3-yl acyclo *C*-nucleoside **209** having a truncated thiosugar residue was synthesized and found to be markedly active against varicella zoster virus (94MI1).

F. IMIDAZO[1,5-*a*]PYRIDINE *C*-NUCLEOSIDES

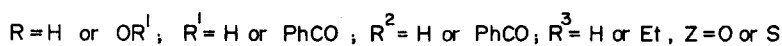
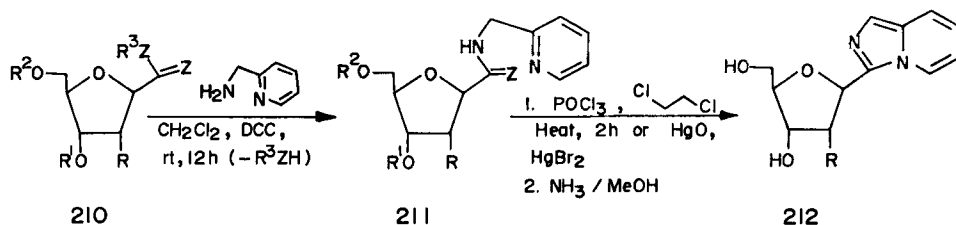
1. Imidazo[1,5-*a*]pyridin-3-yl *C*-Nucleosides

The 2,5-anhydro-D-allonic acid imidate **210** ($R = OR'$, $Z = O$) condensed with 2-aminomethylpyridine to form the corresponding amide **211**. Dehydrative cyclization of the latter gave **212** [84JCS(P1)229]. The reaction was also performed by employing the dithioate **210** ($R = OR'$, $R^3 = H$, $Z = S$) [82MI6; 85JCS(P1)621] (Scheme 63).

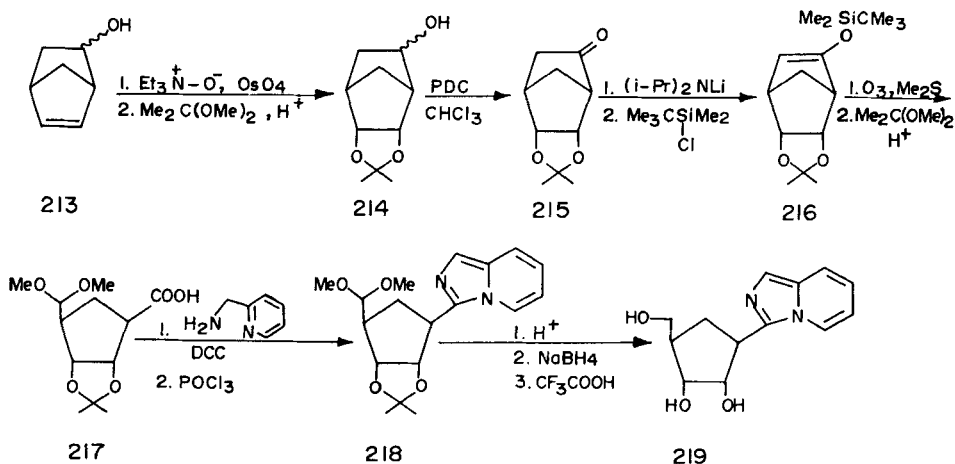
G. IMIDAZO[1,5-*a*]PYRIDINE CARBOCYCLIC *C*-NUCLEOSIDE

1. Imidazo[1,5-*a*]pyridin-3-yl Carbocyclic *C*-Nucleoside

The *C*-nucleoside **219** was prepared from 8,9,10-trinorborn-5-en-2-ol (**213**) according to the total synthetic approach outlined in Scheme 64 [86JCS(P1)393].



SCHEME 63

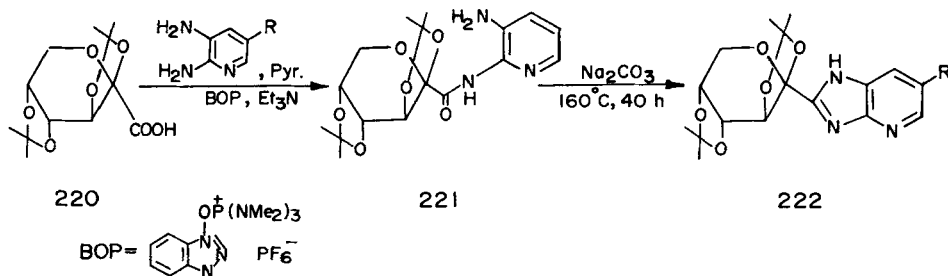


PDC = Pyridine dichromate

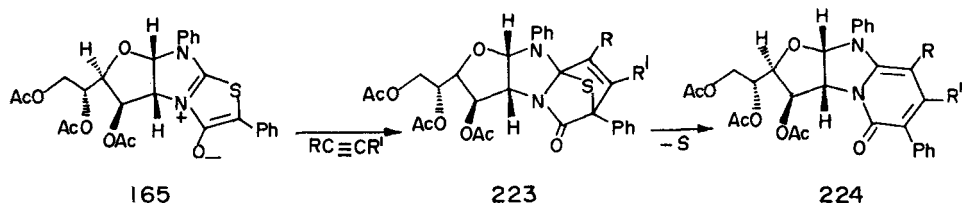
SCHEME 64

H. IMIDAZO[4,5-*b*]PYRIDINE C-NUCLEOSIDES1. *Imidazo[4,5-*b*]pyridin-2-yl C-Nucleosides*

In the presence of a coupling reagent (POB), the D-arabino-hexulosonic acid derivative **220** condensed with 2,3-diaminopyridines to provide the amides **221**. The 2-(β-D-pentopyranosyl)imidazo[4,5-*b*]pyridines **222** were then obtained by mild base-catalyzed cyclodehydration of **221** [80JCS(P1)2683] (Scheme 65).



SCHEME 65



SCHEME 66

I. FURO[2',3':4,5]IMIDAZO[1,2-*a*]PYRIDINE ACYCLO C-NUCLEOSIDES

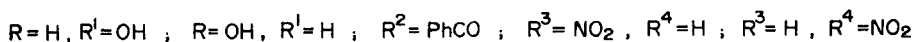
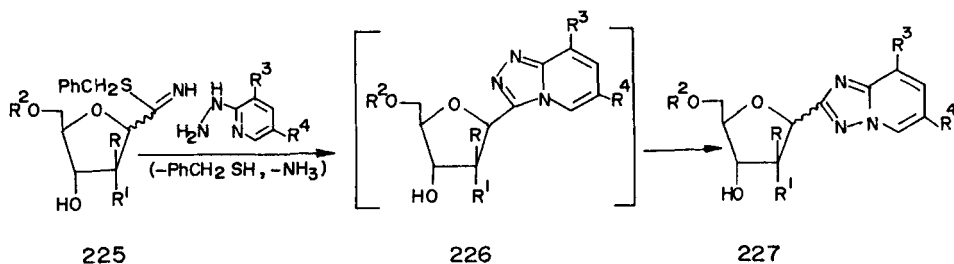
1. *Furo[2', 3':4,5]imidazo[1,2-*a*]pyridin-6-yl Acyclo C-Nucleosides*

Similar to the synthesis of **208**, the furo[2',3':4,5]imidazo[2,1-*b*]thiazolium-3-olate **165** (Section VI,D; Scheme 48) added acetylene carboxylic esters to give **223**, which extruded sulfur to furnish **224** (91MI7) (Scheme 66).

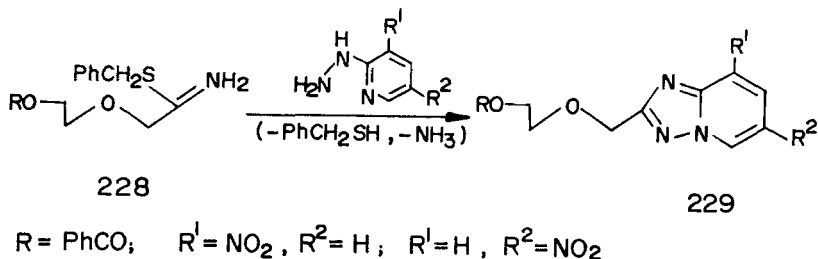
J. 1,2,4-TRIAZOLO[1,5-*a*]PYRIDINE C-NUCLEOSIDES

1. *1,2,4-Triazolo[1,5-*a*]pyridin-2-yl C-Nucleosides*

The initially formed 1,2,4-triazolo[4,3-*a*]pyridin-3-yl *C*-nucleosides **226**, which result from the reaction of the glycosylthioformimidates **225** and 2-hydrazino-3- or 5-nitropyridines, underwent Dimroth rearrangement to the 1,2,4-triazolo[1,5-*a*]pyridin-2-yl *C*-nucleosides **227** (76JOC3124; 78FRP2358154; 79MI1; 81JMC1291), which exhibit antiviral activity against the virus Sindbis (78FRP2358154) (Scheme 67).



SCHEME 67



SCHEME 68

K. 1,2,4-TRIAZOLO[1,5-*a*]PYRIDINE ACYCLO C-NUCLEOSIDES

1. 1,2,4-Triazolo[1,5-*a*]pyridin-2-yl Acyclo C-Nucleosides

Acyclo C-nucleosides **229** were synthesized by cyclocondensation of the thioimidates **228** with 2-hydrazino-3- or 5-nitropyridines (83JHC1169) (Scheme 68).

L. 1,2,4-TRIAZOLO[4,3-*a*]PYRIDINE C-NUCLEOSIDES

1. 1,2,4-Triazolo[4,3-*a*]pyridin-3-yl C-Nucleosides

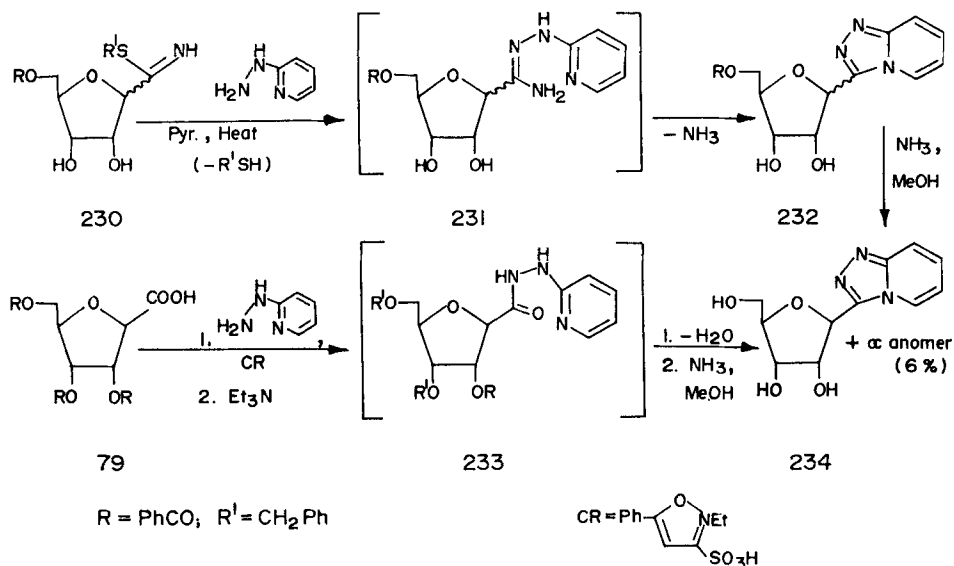
2-Hydrazinopyridines reacted with glycosylthioformimidates (e.g., **230**) (76JOC3124; 79MI1) or 2,5-anhydrohexoaldonic acids (e.g., **79**) (78MI12) to yield, after de-*O*-protection, mixtures of the α - and β -anomers of **234** (Scheme 69).

An interesting synthesis of these C-nucleosides utilized the easily accessible 5-(β -D-ribofuranosyl)tetrazoles **235** as masked C-glycosyl-diazomethane. Reacting **235** with 2-chloro-3-nitropyridine gave a mixture of 1,2,4-triazolo[4,3-*a*]pyridin-3-yl (**236**) and 1,2,4-triazolo[1,5-*a*]pyridin-2-yl (**237**) C-nucleosides. The latter (**237**) resulted from thermally induced Dimroth-like rearrangement of the former (**236**) (86MI9) (Scheme 70). Compounds **236** and **237** possess considerable cytotoxic effect (86MI9).

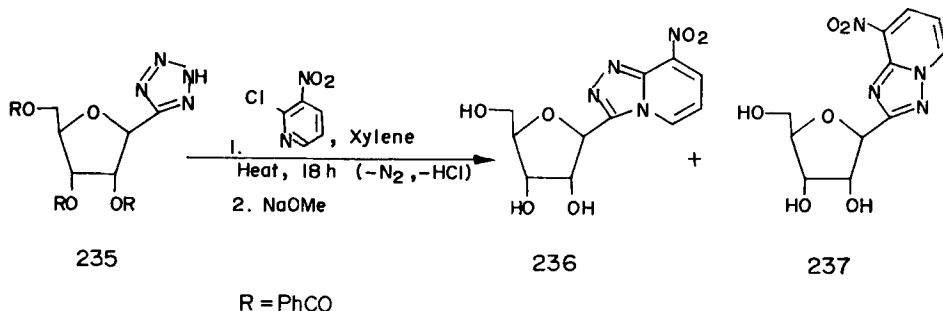
M. 1,2,4-TRIAZOLO[4,3-*a*]PYRIDINE ACYCLO C-NUCLEOSIDES

1. 1,2,4-Triazolo[4,3-*a*]pyridin-3-yl Acyclo C-Nucleosides

As in the preparation of the cyclic analog **236**, the 1,2,4-triazolo[4,3-*a*]pyridin-3-yl acyclo C-nucleoside **239** was obtained, together with the 1,2,4-



SCHEME 69



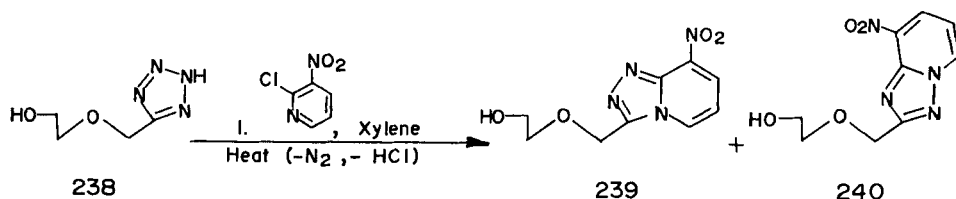
SCHEME 70

triazolo[1,5-a]pyridin-2-yl acyclo C-nucleoside **240**, by reacting the tetrazole acyclo C-nucleoside **238** and 2-chloro-3-nitropyridine (86MI9) (Scheme 71).

N. QUINOLINE C-NUCLEOSIDES

1. Quinolin-2-yl C-Nucleosides

Glycosyl free radicals (**242**), generated by thermolysis (91T6559) or photolysis of 2,5-anhydroaldonic acids (**241**, $R = H$) in the presence of hypervalent iodine compounds (HVICs) [91TL6559; 92TL7575; 93JCS(P1)2417],



SCHEME 71

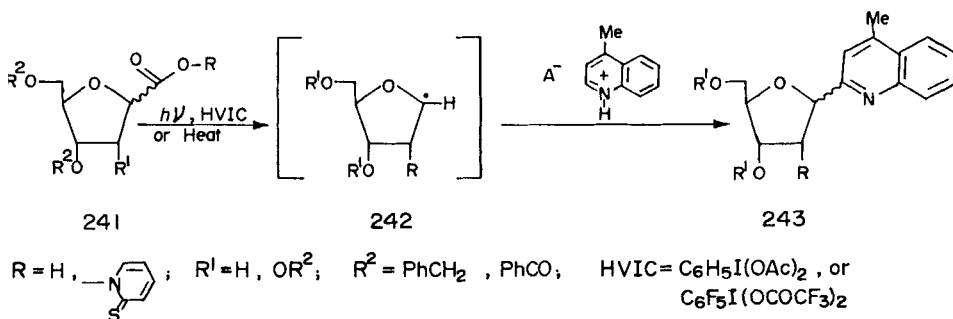
as well as by photolysis of the 2-(thiopyridine)-*N*-(2,5-anhydro-aldonoate) (**241**, $\text{R} = 2\text{-C}_5\text{H}_4\text{NS}$) [91TL3377; 92CL1673; 94JCS(P1)2931], were coupled with lepidinium salts to give mixtures of the α - and β -lepidin-2-yl *C*-nucleosides (**243**). The stereoselectivity of the reaction (α/β ratio) seems to be dependent on the structure of the sugar moiety [94JCS(P1) 2931] (Scheme 72).

2. Quinolin-3-yl *C*-Nucleosides

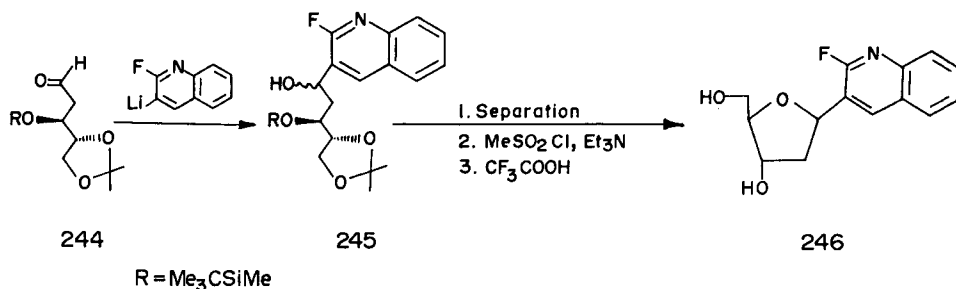
Carbon-carbon bond formation between the *aldehyde*-2-deoxy-D-ribose derivative **244** and 3-lithio-2-fluoroquinoline produced the two diastereoisomers of the quinolin-3-yl acyclo *C*-nucleoside **245**. Separation of the two diastereoisomers, cyclization of their alditolyl chains, and de-*O*-protection gave the 3-(2-deoxy- β -D-ribofuranosyl)quinoline **246** and its α -anomer (91TL3297) (Scheme 73).

3. Quinolin-4-yl *C*-Nucleosides

Elaboration of the 5-hydroxy-5-(β -D-ribofuranosyl)furanone **247** to the 2-carboxamidoquinolin-4-yl *C*-nucleoside **251** was achieved by reaction with aniline as shown in Scheme 74 [93H(36)2805].



SCHEME 72

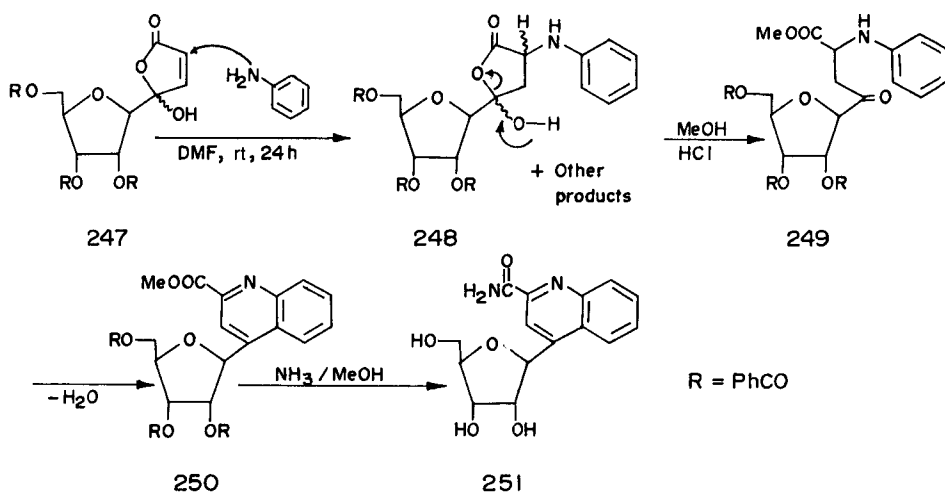


SCHEME 73

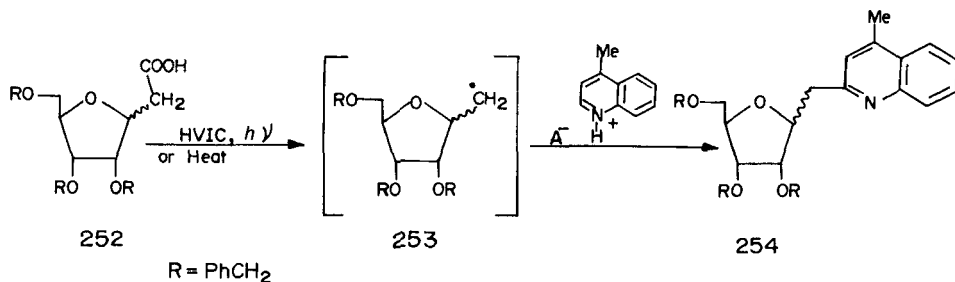
O. QUINOLINE HOMO C-NUCLEOSIDES

1. *Quinolin-2-yl Homo C-Nucleosides*

Togo, Yokoyama, and their co-workers prepared the lepidin-2-yl homo C-nucleoside **254** by C—C bond formation between the D-ribofuranosyl-methyl free radical **253**, generated by photolytic or thermolytic decarboxylation of the D-ribofuranosylacetic acid derivative **252**, in the presence of HVIC, with lepidinium trifluoroacetate (91TL6559) (Scheme 75).



SCHEME 74



SCHEME 75

P. QUINOLINE CARBOCYCLIC C-NUCLEOSIDES

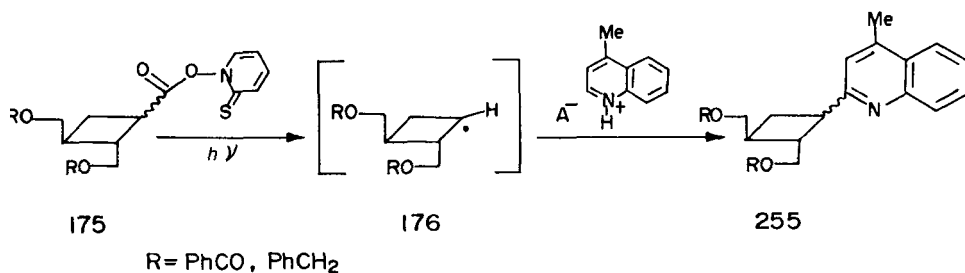
1. Quinolin-2-yl Carbocyclic C-Nucleosides

Coupling the cyclobutane free radical **176** with lepidinium camphor-sulfonate led to the formation of the carbocyclic C-nucleoside **255** [94JCS(P1)2407] (Scheme 76).

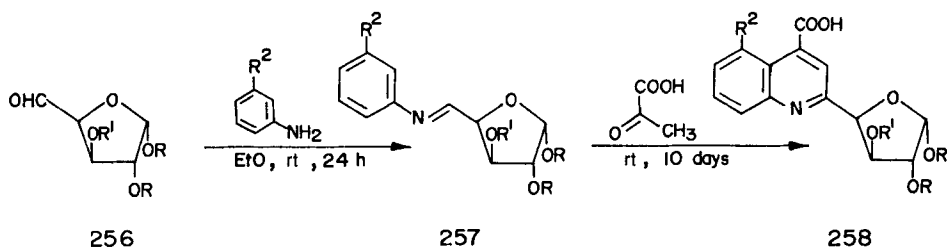
Q. QUINOLINE REVERSE C-NUCLEOSIDES

1. Quinoline-2-yl Reverse C-Nucleosides

The first synthesis of these compounds (**258**) was reported in 1968 by Zhdanov *et al.* (68MI4) by applying the Doebner reaction to Schiff bases **257** of the dialdo-D-xylopentofuranose derivative **256** (Scheme 77). Benzo-[f]quinolin-2-yl reverse C-nucleosides were also similarly prepared by the same group (69ZOB1413).



SCHEME 76



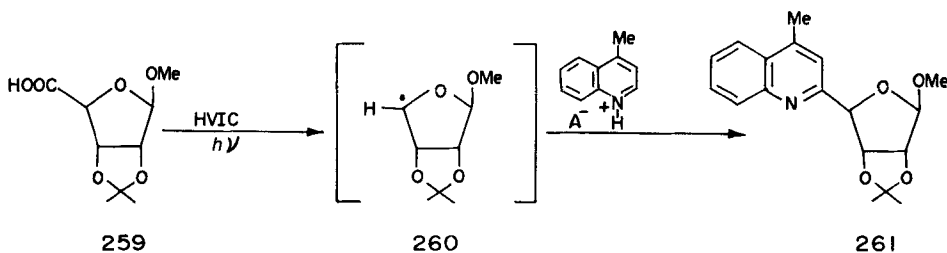
SCHEME 77

Later, some of these C-nucleosides (e.g., **261**) were synthesized by free radical C—C bond formation between the free radical **260**, generated from the D-ribose derivative **259**, and lepidinium trifluoroacetate. Stereoselectivity of this coupling was attributed to the dominance of the steric bulk of the 1,3-dioxolane ring in **260** (92TL7575) (Scheme 78).

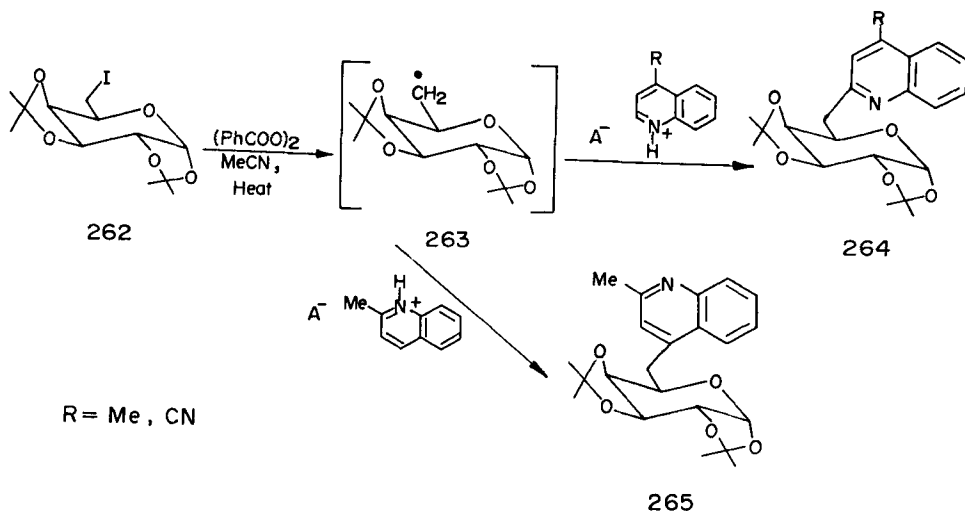
The D-galactopyranose lepidin-2-yl reverse C-nucleoside **264** was obtained by coupling salts of 4-substituted quinolines with the free radical **263** (93JOC959) (Scheme 79).

2. Quinolin-4-yl Reverse C-Nucleosides

Reaction of the free radical **263** with salts of 2-substituted quinolines such as quinaldine trifluoroacetate directed the coupling to position 4 of the quinoline ring system to give **265** (93JOC959) (Scheme 79).



SCHEME 78

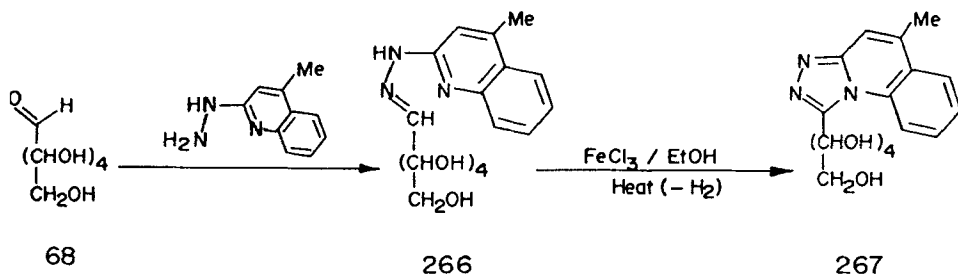


SCHEME 79

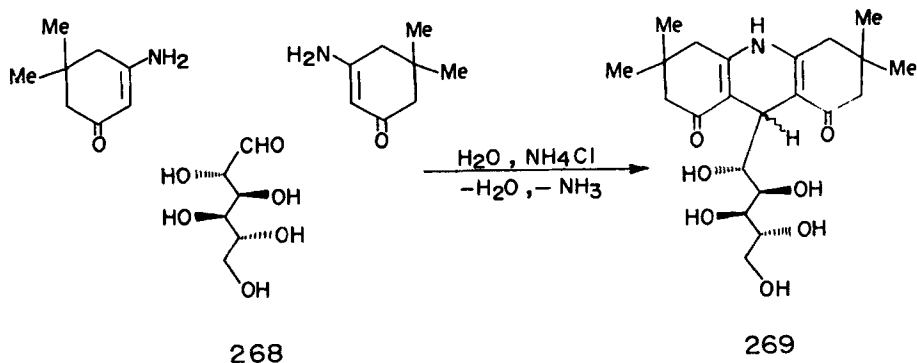
R. 1,2,4-TRIAZOLO[4,3-a]QUINOLINE ACYCLO C-NUCLEOSIDES

1. 1,2,4-Triazolo[4,3-a]quinolin-2-yl Acyclo C-Nucleosides

The 1,2,4-triazole ring of **267** was formed by oxidative cyclization of aldehydo-sugar lepidin-2-yl-hydrazone (**266**) with iron(III) chloride (94MI6) (Scheme 80).



SCHEME 80



SCHEME 81

S. ACRIDINE ACYCLO C-NUCLEOSIDES

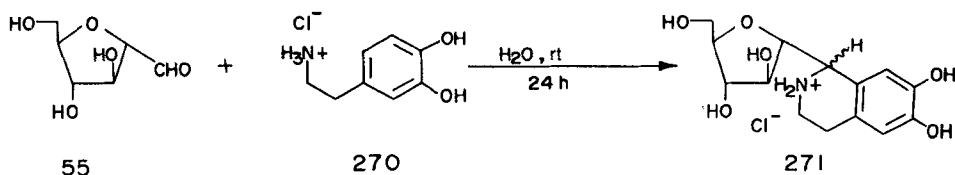
1. *Acridin-9-yl Acyclo C-Nucleosides*

Cyclocondensation of D-mannose (**268**) with two molar equivalents of 3-amino-5,5-dimethylcyclohex-2-en-1-one gave the 9-(D-manno-pentitol-1-yl) acridine-1,8-dione **269** (80MI1) (Scheme 81).

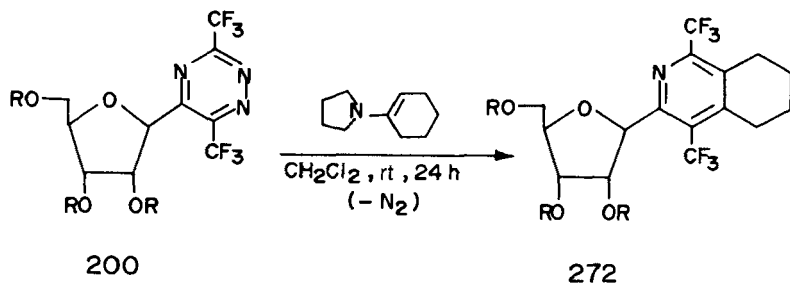
T. ISOQUINOLINE C-NUCLEOSIDES

1. *Isoquinolin-1-yl C-Nucleosides*

Carrying out a Pictet–Spengler reaction between 2,5-anhydro-D-mannose (**55**) and dopamine hydrochloride (**270**) furnished the diastereoisomers of 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolin-1-yl C-nucleoside **271** [83 CJC2721, 83JCS(CC)601] (Scheme 82).



SCHEME 82



SCHEME 83

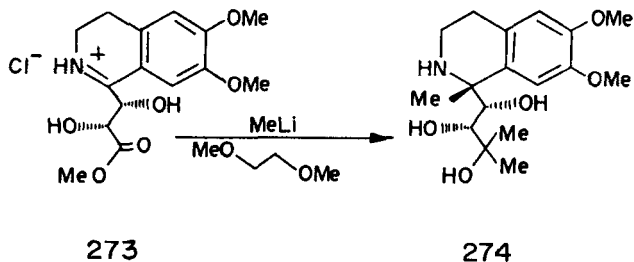
2. Isoquinolin-3-yl C-Nucleosides

Pyrrolidin-1-yl-cyclohexene added to the activated 1,2,4-triazine ring of **200** to form a bicyclic intermediate, which underwent elimination of a nitrogen molecule to give the tetrahydroisoquinolin-3-yl C-nucleoside **272** (95AP175) (Scheme 83).

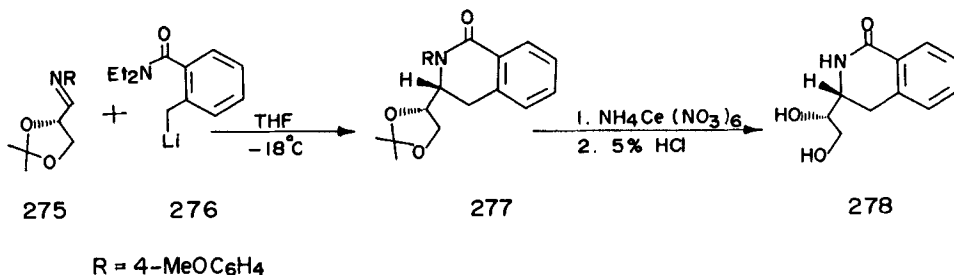
U. ISOQUINOLINE ACYCLO C-NUCLEOSIDES

1. Isoquinolin-1-yl Acyclo C-Nucleosides

The acyclo C-nucleoside **274** having a branched alditolyl chain was obtained upon treatment of the 3-(isoquinolin-1-yl)-L-*threo*-1,2-dihydroxypropanoate **273** with methyllithium (92CJC1555) (Scheme 84).



SCHEME 84



SCHEME 85

2. Isoquinolin-3-yl C-Nucleosides

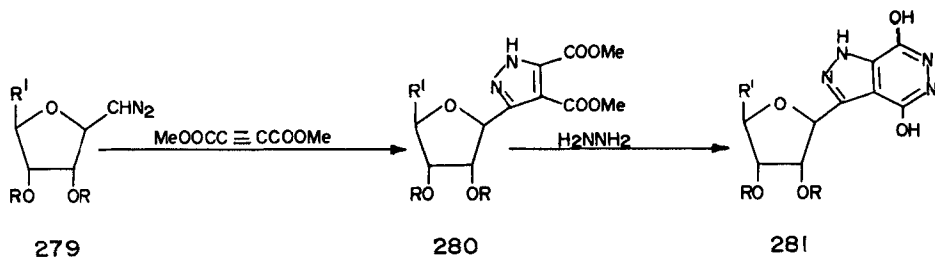
Lithiated 2-(*N,N*-diethylcarboxamido)toluene (**276**) added diastereoselectively to the L-glyceraldehyde imine **275** to afford **277** as a single product; removal of the protective groups led to the free nucleoside **278** [89JC-S(CC)930] (Scheme 85).

X. Condensed 1,2-Diazine C-Nucleosides

A. PYRAZOLO[3,4-*d*]PYRIDAZINE C-NUCLEOSIDES

1. Pyrazolo[4,3-*d*]pyridazin-3-yl C-Nucleosides

Addition of dimethyl acetylene dicarboxylate to the C-glycosyldiazomethanes **279** formed the pyrazol-3-yl C-nucleoside **280**. Annulation of a pyridazine ring to **280** was accomplished by cyclocondensation of their ester groups with hydrazine hydrate to produce **281** [70JCS(CC)313, 70TL4611; 72CCC2798] (Scheme 86).



$\text{R} = \text{PhCH}_2$, $\text{R} + \text{R} = \text{MeCMe}$; $\text{R}^1 = \text{H}, \text{CH}_2\text{OCH}_2\text{Ph}$

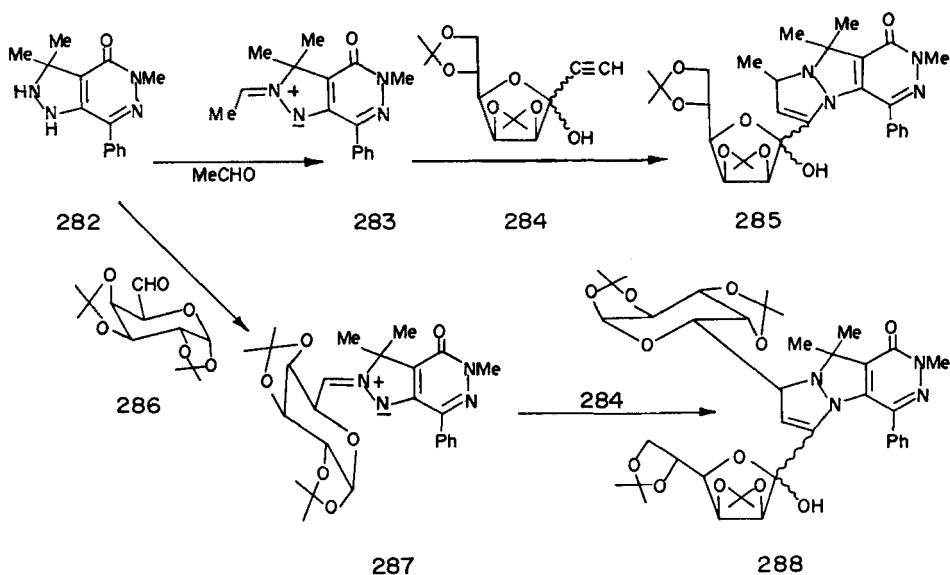
SCHEME 86

B. PYRAZOLO[1',2':1,2]PYRAZOLO[4,3-*d*]PYRIDAZINE C-NUCLEOSIDES1. *Pyrazolo*[1',2':1,2]*pyrazolo*[4,3-*d*]*pyridazin-6-yl C-Nucleosides*

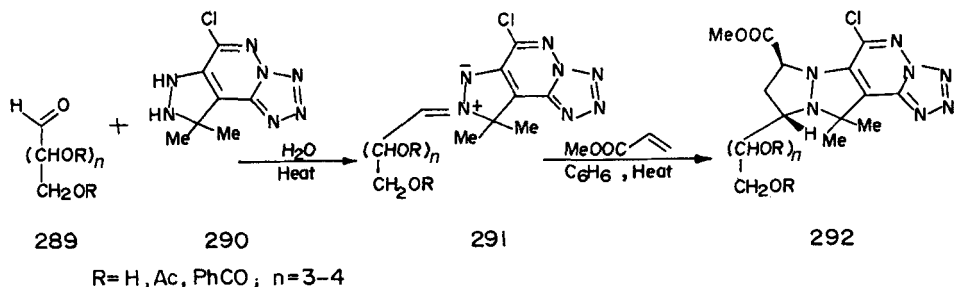
Stereoselective 1,3-dipolar cycloaddition of the azomethine imine **283**, obtained by reacting acetaldehyde and the dihydropyrazolo[4,3-*d*]-pyridazin-4-one **282**, with the acetylenic derivative **284** resulted in the construction of the second fused pyrazole ring of **285**. Condensation of **282** with the dialdoglucopyranose **286** instead of acetaldehyde gave the aldose azomethine imine **287**, which added **284** to give the C-nucleoside **288** carrying two carbohydrate moieties (93FA231) (Scheme 87).

C. PYRAZOLO[1',2':1,2]PYRAZOLO[4,3-*d*]TETRAZOLO[1,5-*b*]PYRIDAZINE ACYCLO C-NUCLEOSIDES1. *Pyrazolo*[1',2':1,2]*pyrazolo*[4,3-*d*]*tetrazolo*[1,5-*b*]*pyridazin-10-yl Acyclo C-Nucleosides*

These acyclo C-nucleosides were prepared by an extension of the just-mentioned approach. The alditol-1-yl azomethine **291** added methyl acrylate to give **292**. The absolute configuration at C8 and C10 of **292** was



SCHEME 87



SCHEME 88

established by single-crystal X-ray analysis, and they were found to be in a *trans* relationship to each other [92T7965; 93FA231, 93JHC(30)1209] (Scheme 88).

D. IMIDAZO[1,5-*b*]PYRIDAZINE C-NUCLEOSIDES

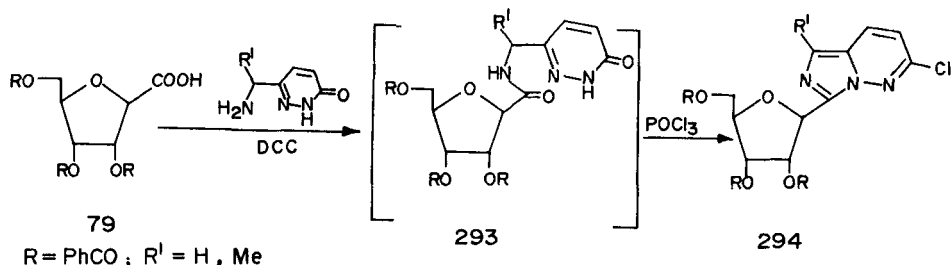
1. Imidazo[1,5-*b*]pyridazin-7-yl C-Nucleosides

The amides **293**, prepared from 2,5-anhydrohexoalonic acids (**79**) and 6-aminomethylpyridazin-3-ones, were cyclodehydrated with phosphoryl chloride to the 2-chloroimidazo[1,5-*b*]pyridazin-7-yl C-nucleosides **294** [82MI6; 84JCS(P1)229; 85JCS(P1)621] (Scheme 89).

E. 1,2,4-TRIAZOLO[4,3-*b*]PYRIDAZINE C-NUCLEOSIDES

1. 1,2,4-Triazolo[4,3-*b*]pyridazin-3-yl C-Nucleosides

When cyclocondensed with 3-hydrazinopyridazine, D-ribofuranosylthioformimide (**230**) gave an anomeric mixture of **295**, which was then separated and de-*O*-protected to the C-nucleoside **296** (81JHC893). Compounds



SCHEME 89

296 were better obtained in the pure β -anomeric form by coupling 3-hydrazinopyridazines with the 2,5-anhydro-D-allonic acid derivative **79** and subsequent cyclodehydration of the formed amides **297**. C-Nucleosides **296** were found devoid of antitumor or antiviral activities (89JMC1547) (Scheme 90).

F. CINNOLINE ACYCLO C-NUCLEOSIDES

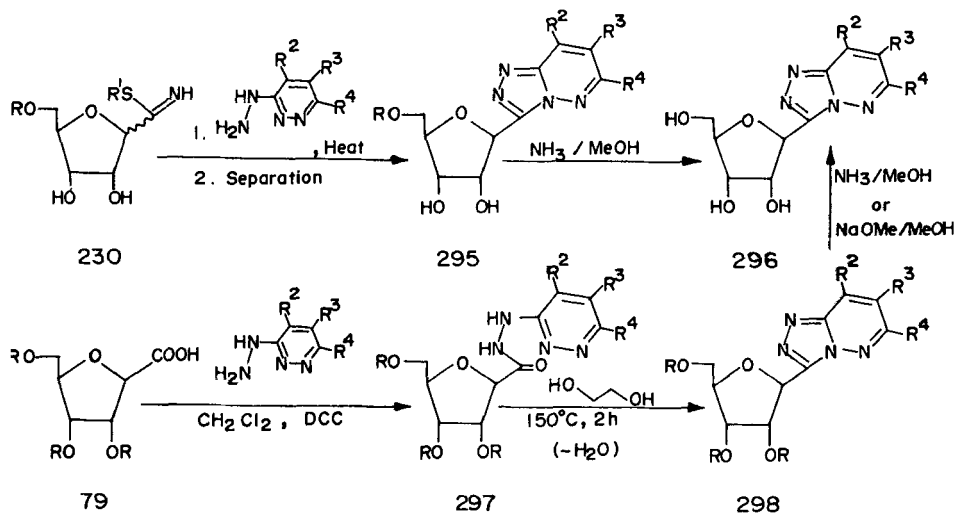
1. Cinnolin-3-yl Acyclo C-Nucleosides

The 3-(D-arabino-tetritol-1-yl)cinnoline **301** was obtained together with the phenyloszone **302** upon heating aqueous acidic solutions of D-glucose or D-mannose (**299**) and phenylhydrazine (63CB2427) (Scheme 91).

G. PHTHALAZINE C-NUCLEOSIDES

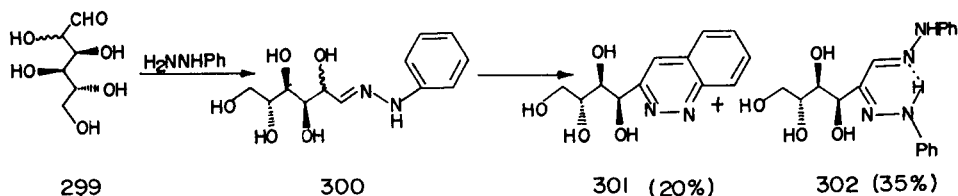
1. Phthalazin-5-yl C-Nucleosides

Aromatization of the Diels-Alder adduct **303**, obtained by addition of dimethylacetylene dicarboxylate to the 2- β -D-ribofuranosylfuran **49**, gave the 6-hydroxy-3- β -D-ribofuranosylphthalate ester **304**, which was O-



$R = \text{PhCO}$; $R^1 = \text{PhCH}_2$; R^2 or $R^3 = \text{H}, \text{Cl}, \text{NH}_2$, $R^4 = \text{Cl}, \text{NH}_2, \text{OH}, \text{OMe}$

SCHEME 90



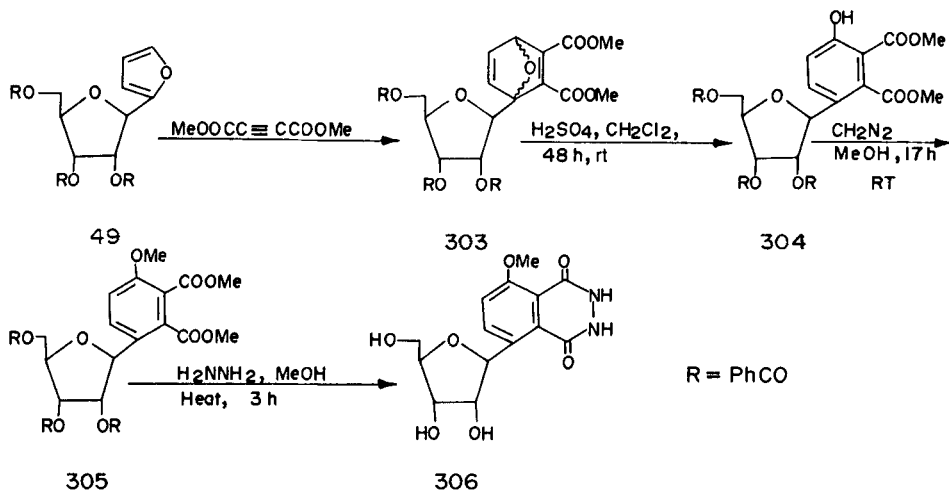
SCHEME 91

methylated to **305**. Cyclization of the two adjacent ester groups of **305** with hydrazine hydrate took place with simultaneous de-*O*-benzoylation of the sugar residue to give the phthalazin-5-yl *C*-nucleoside **306** (85MI8) (Scheme 92).

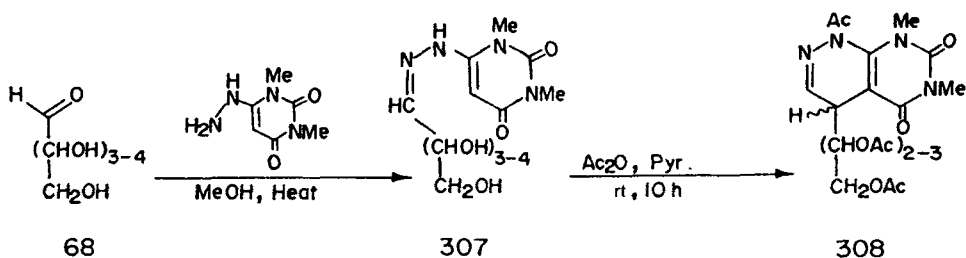
H. PYRIMIDO[4,5-*c*]PYRIDAZINE ACYCLO *C*-NUCLEOSIDES

1. *Pyrimido* [4,5-*c*]pyridazin-4-yl Acyclo *C*-Nucleosides

Aldose pyrimid-6-ylhydrazones (**307**) underwent acetylation together with cyclodehydration to the 4-(poly-*O*-acetyl-alditol-1-yl)pyrimido[4,5-*c*]pyridazines **308** (81CPB629) (Scheme 93).



SCHEME 92



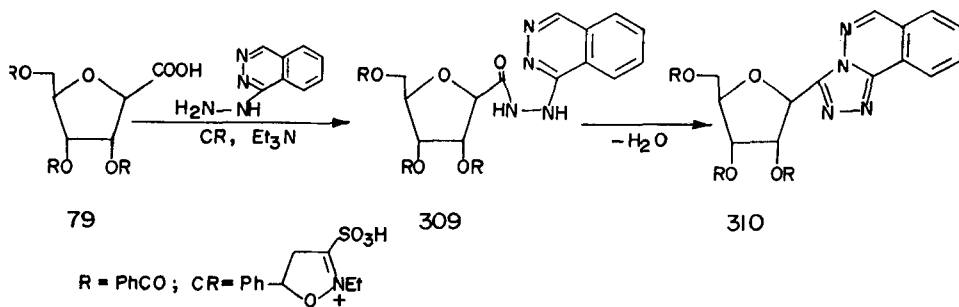
SCHEME 93

I. 1,2,4-TRIAZOLO[3,4-*a*]PHTHALAZINE C-NUCLEOSIDES1. 1,2,4-Triazolo[3,4-*a*]phthalazin-3-yl C-Nucleosides

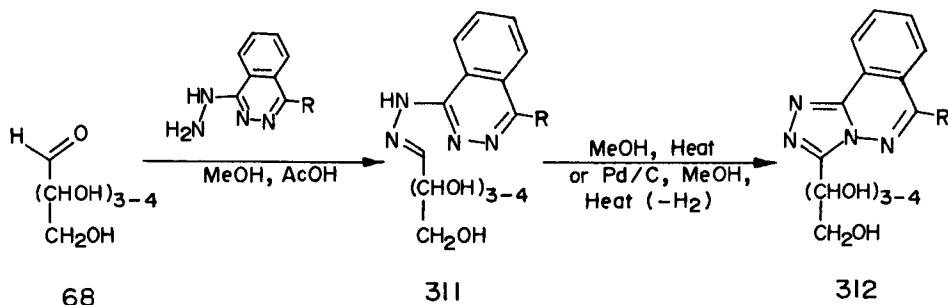
Rosenthal and Lee prepared examples of these C-nucleosides (**310**) by cyclocondensation of the 2,5-anhydro-D-allonic acid **79** with 1-hydrazinophthalazine in the presence of a coupling reagent (CR) (78MI12) (Scheme 94).

J. 1,2,4-TRIAZOLO[3,4-*a*]PHTHALAZINE ACYCLO C-NUCLEOSIDES1. 1,2,4-Triazolo[3,4-*a*]phthalazin-3-yl Acyclo C-Nucleosides

A series of these acyclo C-nucleosides (**312**) were prepared from aldose phthalazin-1-ylhydrazones (**311**), which underwent facile thermal dehydrogenative cyclization to **312**. The cyclization was expedited by catalytic dehydrogenation with palladium on charcoal (81MI5; 83MI8; 89BCJ2701; 91MI9) (Scheme 95).



SCHEME 94



R = H, Ph, PhCH₂

SCHEME 95

Compounds **312** were also prepared by alternative routes that comprised cyclocondensation of aldonolactones (**313**) with 1-hydrazinophthalazines or aldonic acid hydrazides (**315**) with 1-chlorophthalazines. Their acetates **316** were obtained by direct acetylation of **312** or by condensation of aldonyl chloride acetates (**38**) with 1-hydrazinophthalazines (90MI6) (Scheme 96). 1,2,4-Triazolo[3,4-*a*]phthalazin-3-yl acyclo *C*-nucleosides derived from reducing disaccharides were similarly prepared (90MI2).

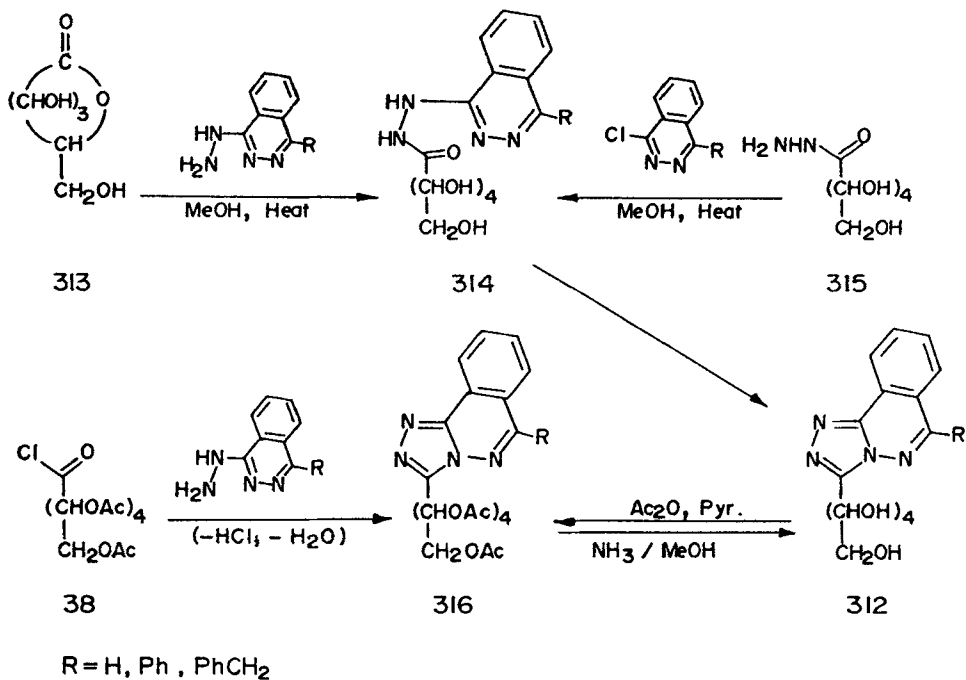
The configuration-conformation relationship of the *O*-acetyl-alditol-1-yl chains of **316** was studied using ¹H NMR (89BCJ2701; 91MI9). Compounds **312** were tested as agrochemicals against some insects, nematodes, and herbs, but were found inactive (89BCJ2701; 91MI9). They served, however, as good corrosion inhibitors of aluminum in acid media (85MI1).

XI. Condensed 1,3-Diazine *C*-Nucleosides

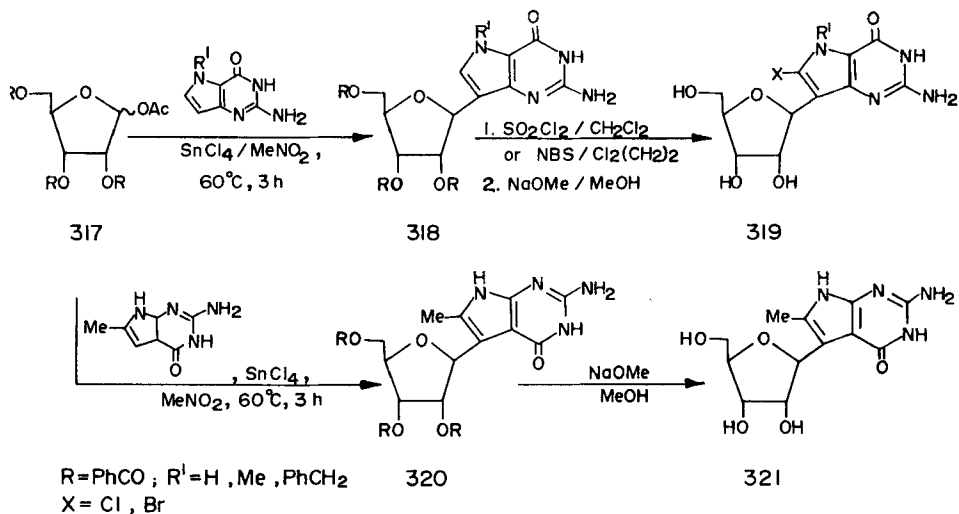
A. PYRROLO[2,3-*d*]PYRIMIDINE *C*-NUCLEOSIDES

1. Pyrrolo[2,3-*d*]pyrimidin-6-yl *C*-Nucleosides

Direct electrophilic, Lewis acid-catalyzed *C*-ribosylation of pyrrolo[2,3-*d*]pyrimidin-4-ones with **317** gave pyrrolo[2,3-*d*]pyrimidin-7-yl *C*-nucleosides **318**. The latter were halogenated at C6 and de-*O*-benzoylated to **319**, which showed good prophylactic activity against the lethal Semliki Forest virus infection in mice (90JMC2750) (Scheme 97).



SCHEME 96



SCHEME 97

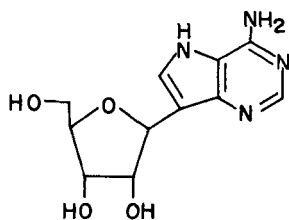
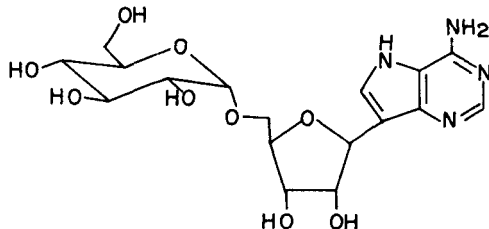
B. PYRROLO[3,2-*d*]PYRIMIDINE C-NUCLEOSIDES

1. *Pyrrolo*[3,2-*d*]pyrimidin-5-yl C-Nucleosides

The previously discussed electrophilic C-ribosylation of **317** with 6-methylpyrrolo[3,2-*d*]pyrimidin-4-one took place at C5, giving **320** as a result of blocking C6 (90JMC2750) (Scheme 97).

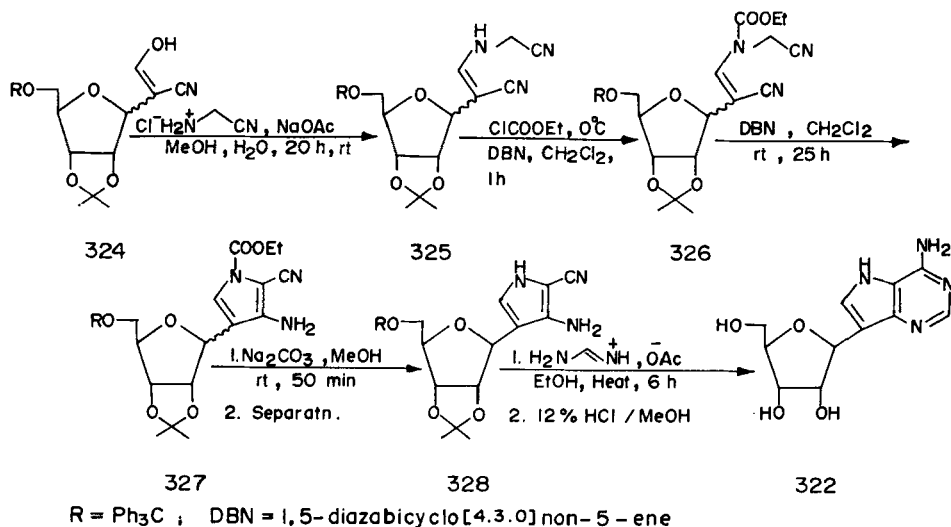
2. *The Naturally Occurring Pyrrolo*[3,2-*d*]pyrimidin-7-yl C-Nucleoside "9-Deazaadenosine"

Rinehart *et al.* (93JA2504) noticed that the aqueous methanolic extract of the lyophilized cells of the cyanobacterium (blue-green alga) *Anabaena affinis* VS-1 exhibited strong cytotoxicity toward L1210 murine leukemic cells. Workup of the extract led to the isolation of two C-nucleosides, which were assigned the structures of 4-amino-7-(β -D-arabino-furanosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (9-deazaadenosine) (**322**) and 4-amino-7-(5'-O- α -D-glucopyranosyl- β -D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (**323**) on the basis of MS, ^1H NMR, ^{13}C NMR, and UV spectral measurements (93JA2504).

**322****323**

The structure of the isolated **322** was further corroborated by direct comparison with synthetic **322**, which was prepared in 1981 by Lim and Klein (81TL25), prior to isolation from the natural source, by a multistep plan that comprised construction of the heterocyclic system by starting from 2-formyl-2- β -D-ribofuranosylacetonitrile (**324**) as shown in Scheme 98 (81TL25). The 2',3'-dideoxy analog of **322** was similarly prepared (96MI2).

C-Nucleoside **322** inhibited the growth of various types of mouse and human leukemic cells (81TL25; 93JA2504), colon carcinoma (83MI1, 83MI3), and nine different human cell tumors (84MI1). Both **322** and



SCHEME 98

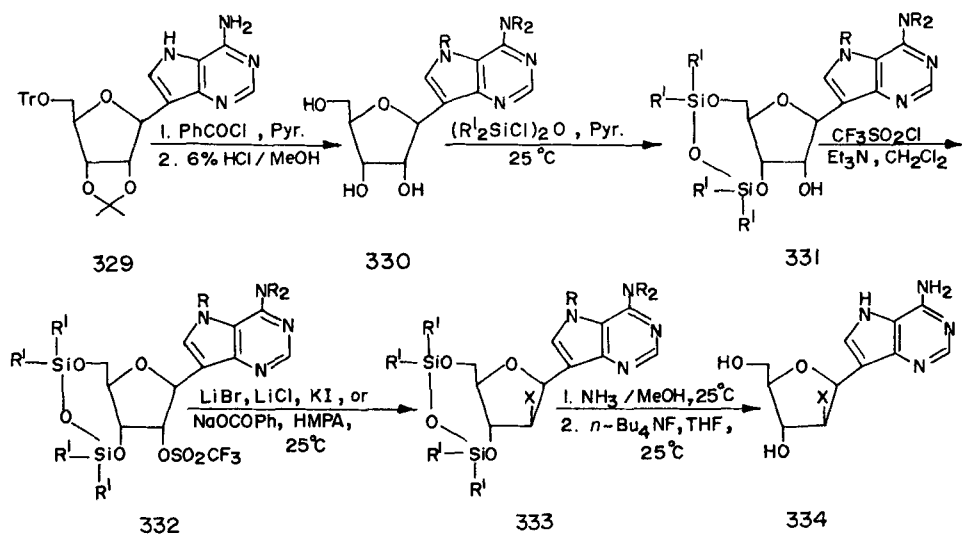
323 were found lethally toxic to the aquatic invertebrate *Ceriodaphnia dubia* (93JA2504).

3. Pyrrolo[3,2-*d*]pyrimidin-7-yl C-Nucleosides

The *O*-protected 9-deazaadenosine derivative **329** was transformed to other pyrrolo[3,2-*d*]pyrimidin-7-yl C-nucleosides (**333** and **334**) by performing alterations in the sugar subunit (86MI11; 93MI7) (Scheme 99). The prepared compounds were active as antileukemic agents, yet were much less active than the parent 9-deazaadenosine (**322**) (86MI11).

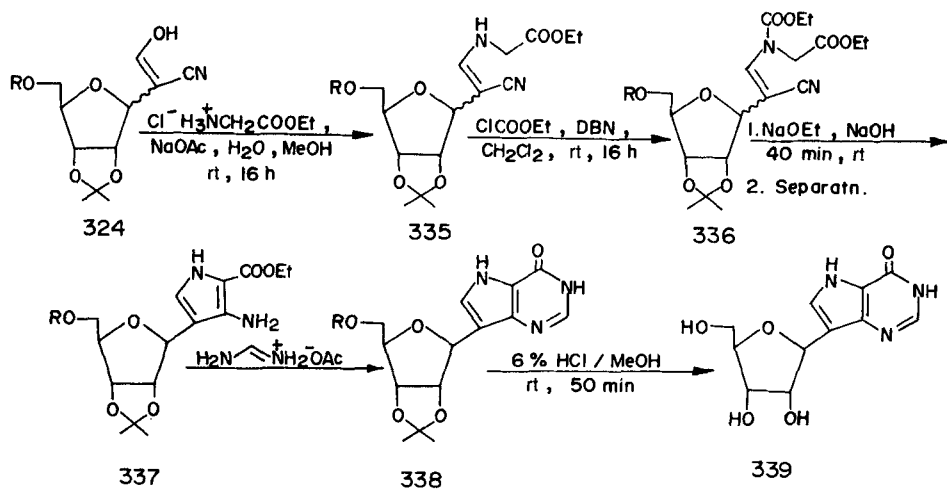
7-β-*D*-Ribofuranosyl-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (9-deazainosine, **339**) is another important C-nucleoside because of the various biological activities it possesses. It was synthesized from **324** as depicted in Scheme 100 (80TL1013; 83JOC780). The 2',3'-dideoxy analog of **339** was prepared by similar reactions (96MI2).

5'-Tritium-labeled 9-deazainosine was obtained by selective de-*O*-tritylation of **338**, oxidation of the resulting C5' primary hydroxyl to an aldehyde function, and then reduction with sodium borotritide (88MI2). 9-Deazainosine (**339**) exhibited antitumor activity against several mouse and human tumor cells (83MI2; 86MI1) and antiprotozoal activity against the pathogenic protozoa *Leishmania donovani*, *T. brucei gambiense*, *Trypanosoma brucei rhodesiense*, *T. cruzi* [84AAC292; 85AAC33, 85JBC(260)9660; 87AAC111, 87AAC1406], and *Giardia lamblia* (86MI2). It also showed



$R = \text{PhCO}$, $R' = \text{Me}_2\text{CH}$, $X = \text{Br}, \text{Cl}, \text{I}, \text{PhCOO}$.

SCHEME 99



$R = \text{Ph}_3\text{C}$

SCHEME 100

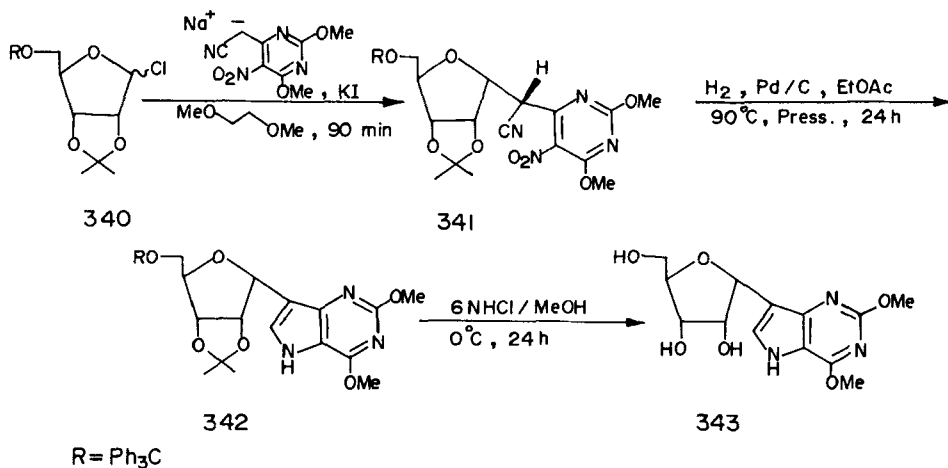
antibacterial properties against *Pneumocystis carinii* pneumonia in immunosuppressed rats (86AAC181; 87MI1) and has been suggested as a promising drug for the treatment of this disease, frequently encountered in immunosuppressed patients and in patients with AIDS (87MI1).

2,4-Dimethoxy-7- α -D-ribofuranosylpyrrolo[3,2-*d*]pyrimidine **343** was synthesized through ionic C—C bond formation by coupling the carbanion of the active methylene group of 6-cyanomethyl-2,4-dimethoxy-5-nitropyrimidine and the D-ribofuranosyl chloride **340**. The resulting **341** was cyclized to **342** by catalytic reduction and then deprotected to **343** (86JOC1058) (Scheme 101).

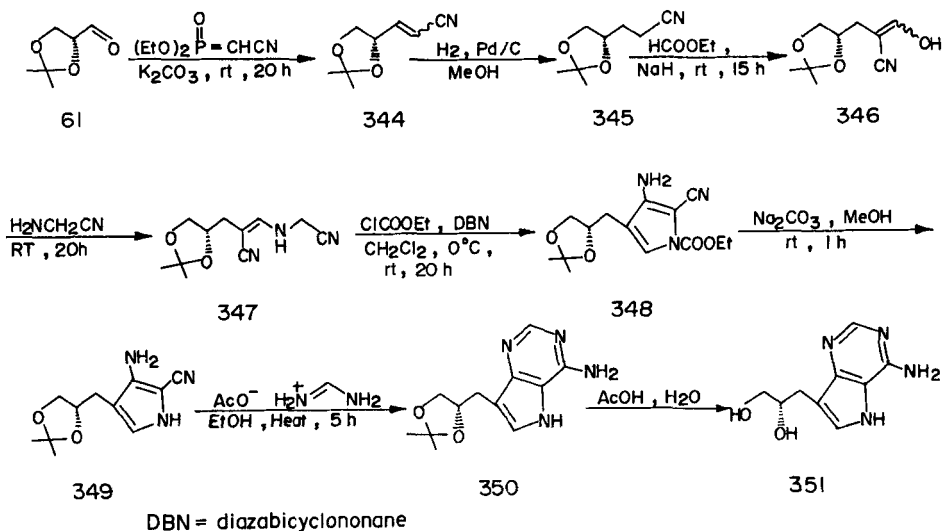
C. PYRROLO[3,2-*d*]PYRIMIDINE ACYCLO C-NUCLEOSIDES

1. Pyrrolo[3,2-*d*]pyrimidin-7-yl Acyclo C-Nucleosides

A number of 9-deazaadenosine acyclo C-nucleosides carrying different polyhydroxyalkyl chains (e.g., **351**) were prepared by Buchanan and his group from 3-amino-2-cyanopyrrol-4-yl acyclo C-nucleosides (e.g., **349**) through construction of their fused pyrimidine rings. Unfortunately, none of these compounds was found active against representative RNA and DNA viruses in cell cultures [91JCS(P1)195] (Scheme 102).



SCHEME 101



SCHEME 102

D. Furo[3,2-*d*]PYRIMIDINE C-NUCLEOSIDES

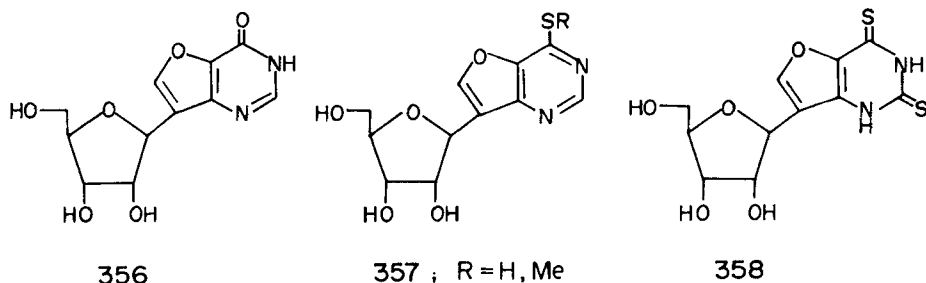
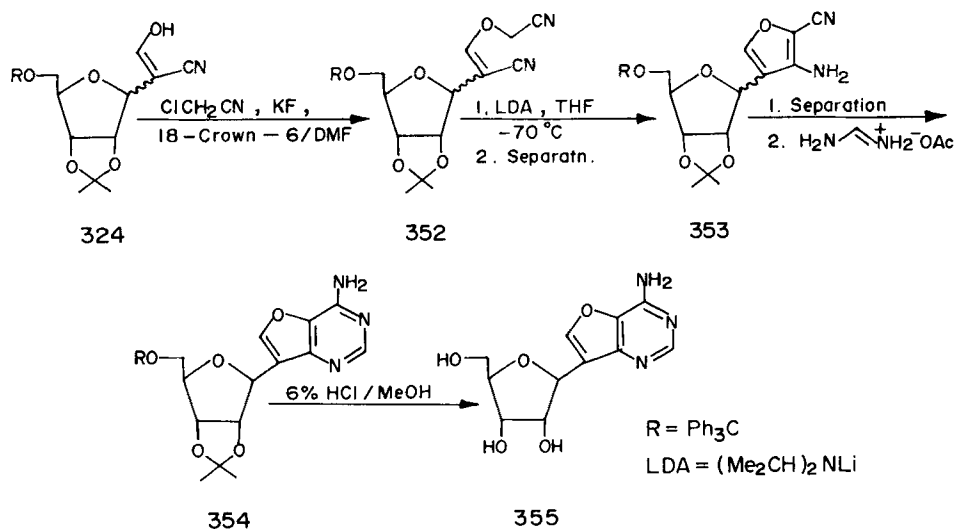
1. The Naturally Occurring Furo[3,2-*d*]pyrimidin-7-yl C-Nucleoside "Pyrrolosine"

Searching for RNA inhibitors from natural sources, Ikegami *et al.* isolated a compound from the culture broth of *Streptomyces alba* A282 that halted embryonic development in starfish (*Asterina pectinifera*) as a result of inhibiting RNA synthesis (90JA9668). Studying the MS, UV, ^1H NMR, ^{13}C NMR, and X-ray diffraction data of the isolated compound, the same group concluded that the structure of this compound is 7- β -D-ribofuranosylpyrrolo[3,2-*d*]pyrimidin-4-one (9-deazainosine, **339**) and named it "pyrrolosine." Physical and biological properties of the isolated compound, however, were found (90JA9668) to be different from those of **339**, which was synthesized by Klein and his group prior to the isolation of pyrrolosine (80TL1013; 83JOC780) (Section XI,B,3). Accordingly, pyrrolosine was reinvestigated and the results were published 2 years later by both the American (92JA668) and the Japanese groups (92MI1), who revised the structure to 4-amino-7- β -D-ribofuranosylfuro[3,2-*d*]pyrimidine (7-oxa-7,9-dideazaadenosine, **355**). The erroneous elucidation of structure was attributed (92JA668, 92MI1) to misinterpretation of X-ray data (90JA9668), and a suggestion has been made to rename pyrrolosine in a way that reflects the actual structure

(92JA668). The revised structure was further established (92JA668) by direct comparison with synthetic **355** prepared as shown in Scheme 103 (86TL815; 90MI8).

In addition to inhibition of RNA synthesis, pyrrolosine inhibited growth of transformed human fibroblast KMST-6 cells and mouse mammary carcinoma FM3A cells (90JA9668). However, it was 10-fold less active than 9-deazaadenosine **322** against mouse L1210 (86TL815; 90MI8) and P815 leukemia cells *in vitro* (86TL815).

The inosine **356**, thioinosine **357**, and dithioxanthosine **358** analogs of **355** were also prepared from **324** by synthetic plans comparable to that depicted in Scheme 103 (90MI8). The inosine analog **356** exhibited activity against the pathogenic protozoa *Leishmania donovani* and *Trypanosoma gambiense* (90MI8).



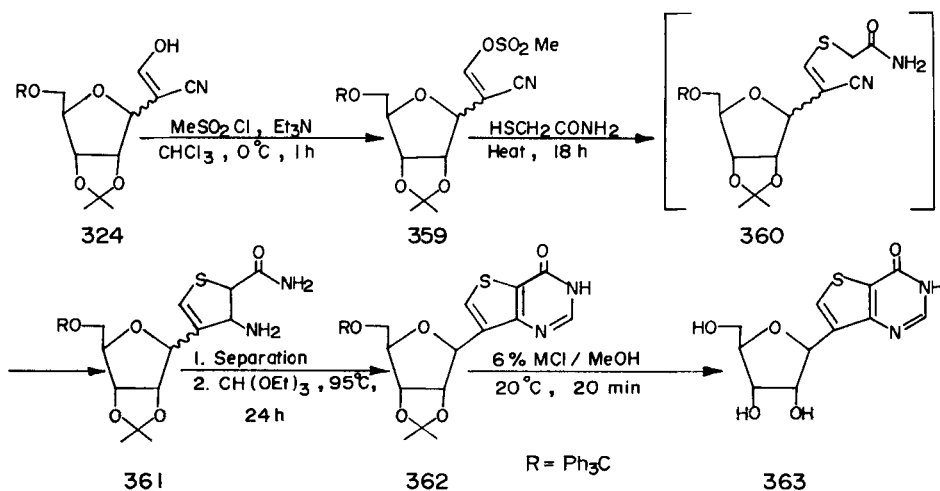
E. THIENO[3,2-*d*]PYRIMIDINE C-NUCLEOSIDES1. Thieno[3,2-*d*]pyrimidin-7-yl C-Nucleosides

7- β -D-Ribofuranosyl[3,2-*d*]pyrimidin-4(3*H*)-one (7-thia-7,9-dideazainosine, **363**) was synthesized from **324** by the multistep elaboration of both rings of its heterocyclic system as detailed in Scheme 104 (82JOC4633). C-Nucleoside **363** significantly inhibited growth of L1210 and P815 leukemia cells in mice (82JOC4633), revealed antiprotozoal activity against *Leishmania donovani* [85JBC(260)9660], and very weakly inhibited human erythrocytic nucleoside phosphorylase (86MI1).

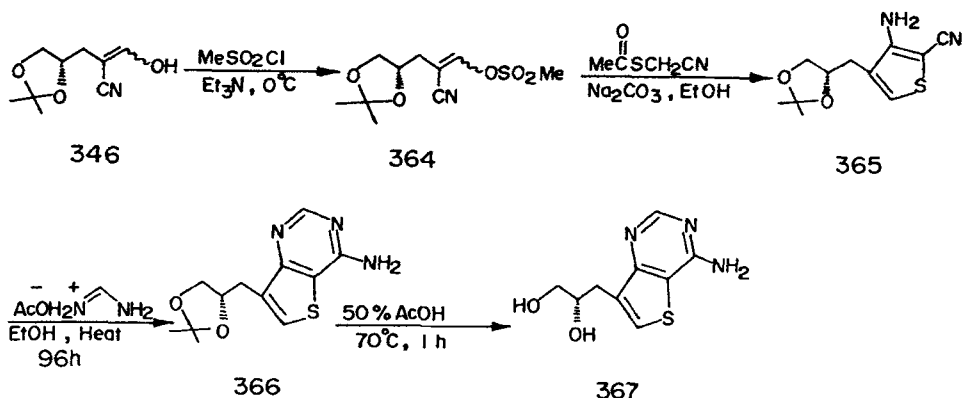
3',5'-Di-*O*-protection of **363** and deoxygenation of C2' OH gave its 2'-deoxy analog (86MI11).

F. THIENO[3,2-*d*]PYRIMIDINE ACYCLO C-NUCLEOSIDES1. Thieno[3,2-*d*]pyrimidin-7-yl Acyclo C-Nucleosides

The thieno[3,2-*d*]pyrimidine system of **367** was constructed onto the acyclic sugar derivative **346**. This acyclo C-nucleoside (**367**) did not inhibit a number of DNA and RNA viruses in cell cultures [91JCS(P1)195] (Scheme 105).



SCHEME 104



SCHEME 105

G. THIENO[3,4-*d*]PYRIMIDINE C-NUCLEOSIDES

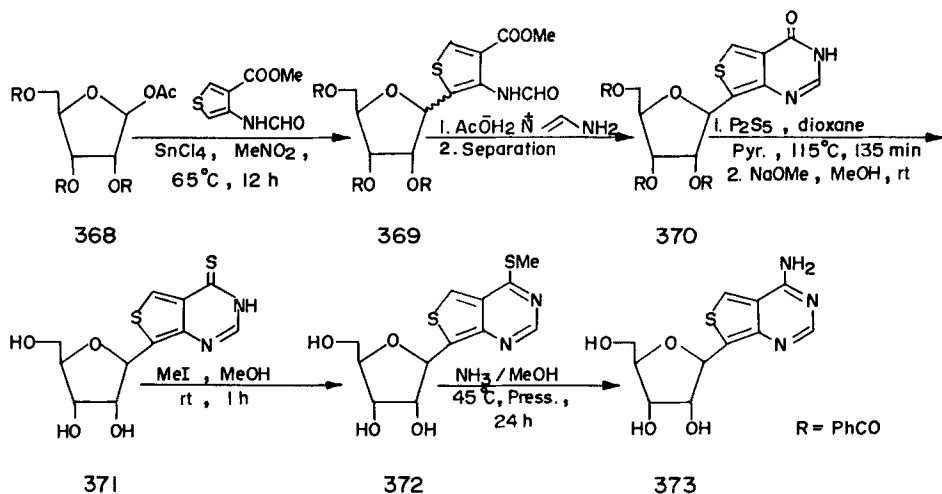
1. Thieno[3,4-*d*]pyrimidin-7-yl C-Nucleosides

Under the catalytic effect of tin(IV) chloride, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- α -D-ribofuranose (**368**) regiospecifically C-glycosylated 4-formamido-3-methoxycarbonylthiophene at C5 to give a mixture of the two anomers of **369**. Annulation of the pyrimidine ring of the 6-thia-7,9-dideazainosine **370** was achieved by reacting **369** with formamidine acetate [88TL3537; 90MI7; 93JHC(30)509]. C-Nucleoside **370** was further elaborated to the adenosine analog **373** (Scheme 106) and the 6'-iodo-6'-deoxyinosine analog **375** (Scheme 107) [93JHC(30)509]. Compounds **370** and **372** proved cytotoxic to L1210-Cl, sarcoma 180, and HL60 tumor cell lines, whereas **375** effectively inhibited purine nucleoside phosphorylase [93JHC(30)509].

H. PYRAZOLO[1,5-*a*]PYRIMIDINE C-NUCLEOSIDES

1. Pyrazolo[1,5-*a*]pyrimidin-3-yl C-Nucleosides

In basic media, 1,3-dimethyluracil transferred an α , β -unsaturated keto moiety to the 3-aminopyrazol-4-yl C-nucleoside **376**, providing the complementary carbon fragment to annulate the pyrimidine ring of **377**. Removal of the *O*-protective groups of **377** with methanolic hydrochloric acid caused

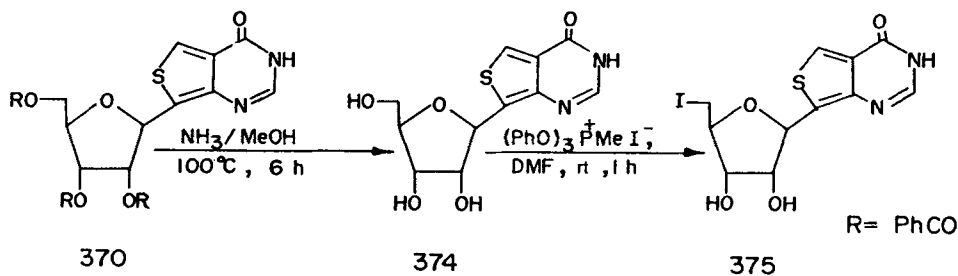


SCHEME 106

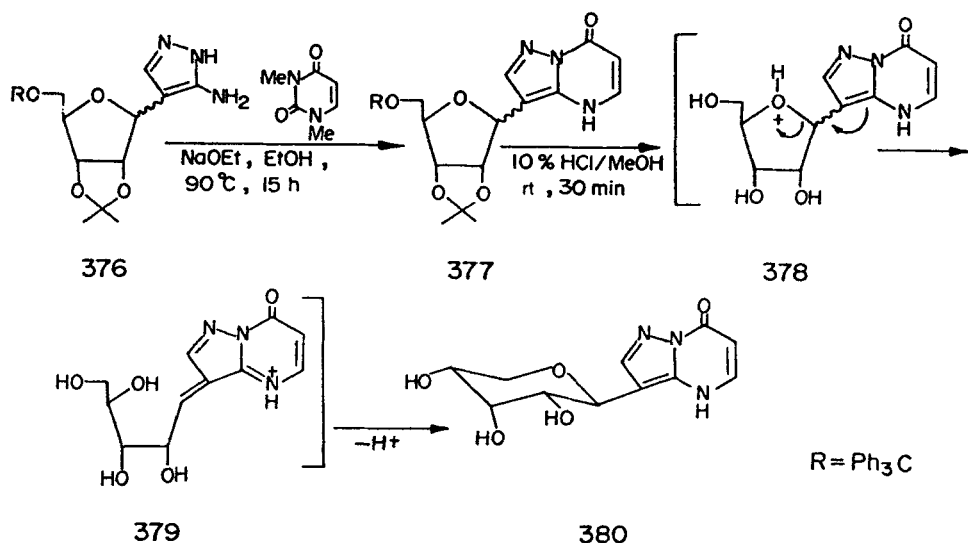
sugar ring enlargement to afford the 3- β -D-ribofuranosylpyrazolo[1,5-*a*]pyrimidin-7-one **380** (86JHC349) (Scheme 108).

2. Pyrazolo[1,5-*a*]pyrimidin-7-yl C-Nucleosides

Cyclocondensation of the C-glycoside enaminone **381** with 3-aminopyrazole and removal of the protective groups gave the C-nucleoside **382** [95H(41)507] (Scheme 109).



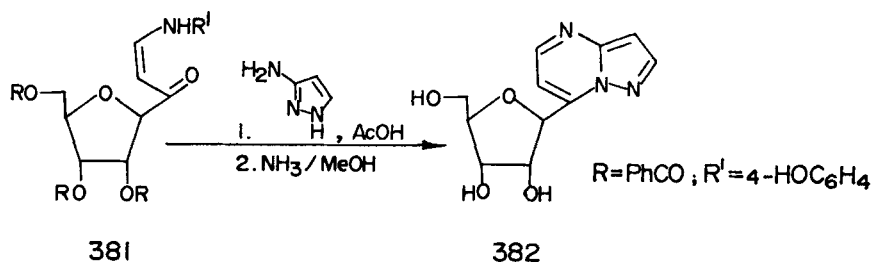
SCHEME 107



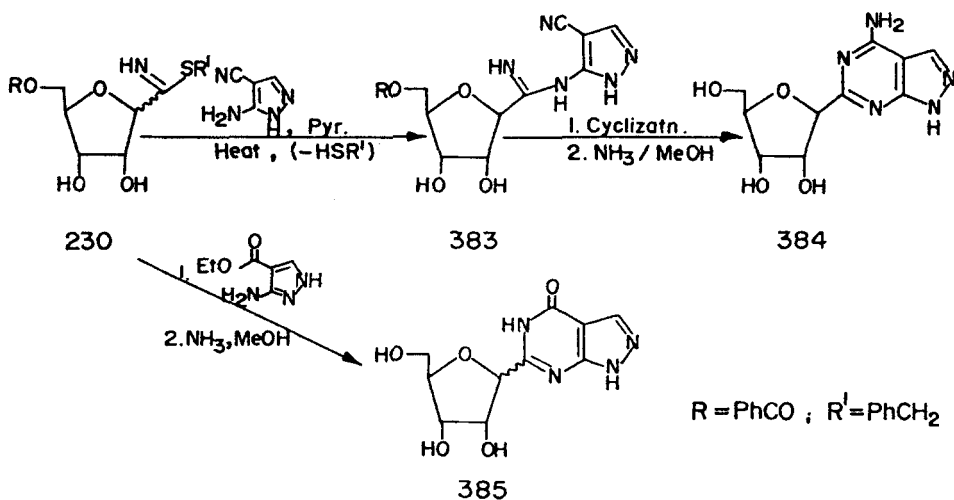
SCHEME 108

I. PYRAZOLO[3,4-*d*]PYRIMIDINE C-NUCLEOSIDES1. *Pyrazolo[3,4-*d*]pyrimidin-6-yl C-Nucleosides*

Cyclocondensation of the ribofuranosylthioformimidates **230** with 3-amino-4-cyanopyrazole gave, stereospecifically, the 6-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidin-4-one **385** [73JCS(CC)680]. However, the reaction with 3-amino-4-ethoxycarbonylpyrazole was stereoselective to give the two anomers of **385**; the β-anomer preponderated (75JOC2825) (Scheme 110).



SCHEME 109



SCHEME 110

J. PYRAZOLO[4,3-*d*]PYRIMIDINE C-NUCLEOSIDES

1. The Naturally Occurring Pyrazolo[4,3-*d*]pyrimidin-3-yl C-Nucleosides "Formycin," "Formycin B," and Their Congeners

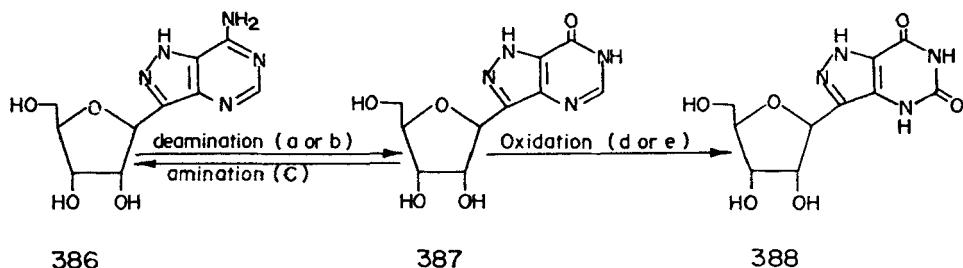
The antibiotic formycin was first isolated in 1964 from culture filtrates of the protoactinomycete *Nocardia interforma* [64JAN(A)96; 66JAP66/17629; 83MI11]. Formycin, together with another related C-nucleoside, formycin B (laurusin), was also isolated from the same organism in 1965 [65JAN(A)175] and from *Streptomyces lavendula* at the early stage of culture growth (65ABC375). The amount of formycin B increased while that of formycin decreased until it disappeared with aging of *S. lavendula* cultures, which implied that formycin might be the precursor of formycin B (65ABC375). Other streptomycetes, namely, *Streptomyces* S-685 (67JAN(A)49), *S. gunamaences* (67JAP67/10928), and *S. M406-A-1* (74JAN909; 75JAN965), also produced formycin.

The 7-amino-3-β-D-ribofuranosylpyrazolo[4,3-*d*]pyrimidine structure **386** of formycin (the C-nucleoside isoster of adenosine) and 3-β-D-ribofuranosylpyrazolo[4,3-*d*]pyrimidin-7-one structure **387** of formycin B (the C-nucleoside isoster of inosine) were elucidated on the basis of degradation [66JAN(A)91], UV, ¹H NMR [66JHC110; 77ZN(C)528], and MS results

(69JHC459). Formycin (**386**) can be deaminated to formycin B (**387**) both chemically by treatment with acids (65ABC377) or sodium nitrite [65JAN(A)178] and enzymatically by adenosine deaminase from various sources [65ABC377, 65JAN(A)175, 65JAN(A)178, 65JAN(A)191; 68JAP68/759; 69BBA(174)696, 69JBC(244)3243; 75MI1). However, amination of formycin B (**387**) to formycin (**386**) was made by adenylosuccinic synthetase from *Pseudomonas fluorescenes* and *Streptomyces kasugaensis* (68JAN334) (Scheme 111).

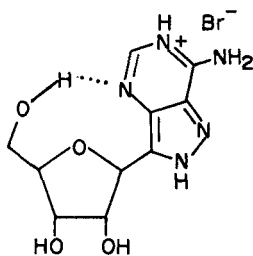
Oxoformycin B, 3- β -D-ribofuranosylpyrazolo[4,3-*d*]pyrimidine-5,7-dione (**388**) (the C-nucleoside isoster of xanthosine), was isolated from urine of rabbit and mice injected with formycin (**386**) or formycin B (**387**) (68JAN1, 68MI1) as a result of biological oxidation with hepatic aldehyde oxidase (69JAN36; 70MI3). *Nocardia interforma* and *Streptomyces kasugaensis* are able to transform formycin B (**387**) to oxoformycin B (**388**) by oxidation with xanthine oxidase (68JAN334).

X-ray analysis of formycin hydrobromide monohydrate revealed its existence in the classical *syn* conformation **389** in which N6 is protonated, H1 migrated to N2, and an H-bond is formed between O5' and N4 [66TL597; 74AX(B)1511; 75ANY3]. The conformation of formycin monohydrate, however, was found to be intermediate between the classical *anti* and *syn* conformations (68PNA1494; 73B1196; 75ANY3). Conformations of formycin B and oxoformycin B were found to correspond to the *anti* form **390** and the *syn* form **391**, which is stabilized by an intramolecular N4-H \cdots O5' H-bond, respectively [76AX(B)813].

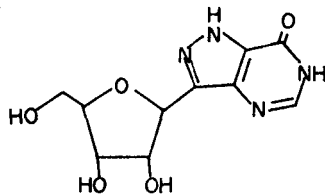


a, acid or $\text{NaNO}_2 + \text{H}^+$; b, adenosine deaminase; c, adenylosuccinic synthetase; d, xanthine oxidase; e, hepatic aldehyde oxidase

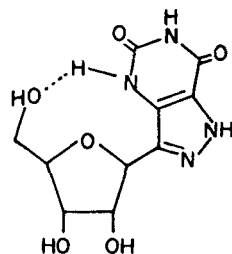
SCHEME 111



389

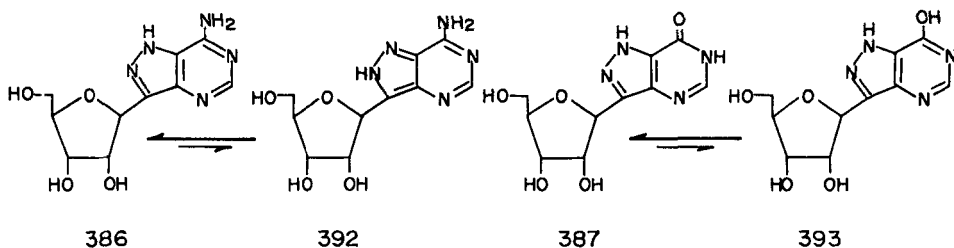


390



391

^1H and ^{13}C NMR measurements (73JA4761, 73JHC431; 76JA4736; 84MI10) indicated the predominance of the N1-H tautomer (**386**) over the N2-H (**392**) tautomer for formycin and the amide form (**387**) over the imidic acid form (**393**) for formycin B.

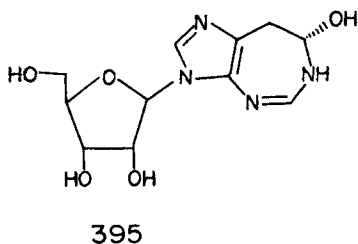
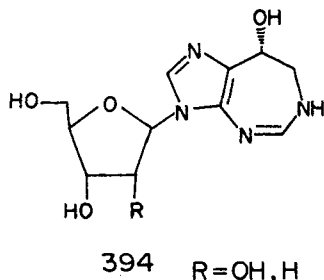


Fluorescence [69JBC(244)1228; 77JHC135] and luminescence (82MI2) spectra of formycin, as well as fluorescence and ORD spectra of oxoformycin B [75ZN(C)835], were studied.

Biosynthetic studies pinpointed the importance of lysine and glutamate during the biosynthesis of formycin [71JAN(A)253, 71PAC489; 74JAN909; 76JAN638; 79JBC(254)8819; 80JCS(CC)917].

Because of their isosteric relationship, formycin can replace adenosine in many biochemical processes (biological mimicking) [67JBC(242)3868; 68BBA(155)82, 68BBA(174)696, 68JBC(243)3214, 68MI2; 69MI1, 69MI2, 69PNA581; 70PNA539; 72JBC(247)4014; 74MI2; 75JAN965; 79MI2, 79MI3, 79MI4]. Consequently, formycin displays a wide range of biological activities (70MI2; 75MI4; 78MI11; 79MI4; 81MI2; 82MI1; 83MI3). Among these activities are antiviral [66JAN(A)286; 67JAN(A)49, 67JAN(A)129, 67JAN(A)297; 75MI2; 85MI2], antibacterial [64JAN(A)96; 65JAN(A)178, 65JAN(A)259; 66JAP66/17629; 67JAN(A)308, 67JAP67/21755; 68JBC(243)3532; 78B2350], and antiprotozoal against *Schistosoma mansoni* (74MI1), *Trypanosoma cruzi* (the causative agent to Chaga's disease)

(83MI5), *Leishmania donovani* [81BBR(100)1377], and *L. tropica* (83AAC233). Formycin inhibited also the growth of various types of tumors [64JAN(A)96, 64JAN(A)124; 65JAN(A)259; 66JAP66/17629; 67JAN(A)227, 67JAN(A)277, 67MI1, 67MI2; 68JAN5; 69MI1], increased vascular permeability in rat skin [67JAN(A)369], and selectively inhibited low-molecular-weight RNA [73BBA(312)292]. Unfortunately, many of these activities diminish with time because of the ready conversion of formycin to the much less active formycin B by adenosine deaminase (ADA) (76MI1). In the presence of coformycin {6,7,8-trihydro-8-hydroxy-3- β -D-ribofuranosylimidazo[4,5-*d*]1,3-diazepine (**394**, R = OH)}, 2'-deoxycorformycin (**394**, R = H), or isocorformycin (**395**), the deamination of formycin by ADA is strongly inhibited and the biological activities are enhanced [67JAN(A)227, 67JAN(A)308; 75MI3; 76MI1; 77MI1; 78MI1; 80JAN303].

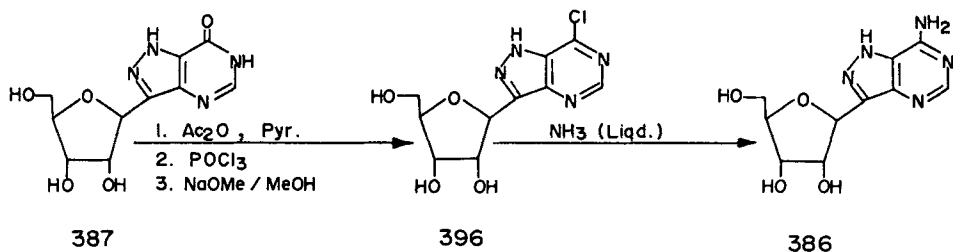


Albeit of less pronounced magnitude, formycin B possesses antiviral [66JAN(A)286; 67JAN(A)129; 75MI2], antibacterial [65ABC375, 65JAN(A)175, 65JAN(A)178, 65JAN(A)259; 68JAN264], antiprotozoal [81BBR(100)1377; 82BBR(108)349; 83AAC233, 83PNA288; 85JBC(260)9660], and antitumor activities [65JAN(A)259; 68JAN5].

The first synthesis of formycin (**386**) was reported in 1971 using the nucleoside–nucleoside transformation approach [71JCS(C)2443]. Formycin B (**387**) was *O*-acetylated and transformed to the 6-chloropyrazolo[4,3-*d*]pyrimidin-3-yl derivative **396**. Amination of **396** with liquid ammonia gave formycin (**386**) (Scheme 112).

Synthesis of formycin by the stepwise assembly of the pyrazolopyrimidine system onto the sugar moiety was accomplished by Kalvoda in Czechoslovakia (78CCC1431). The starting material utilized in this synthesis was the 3-cyano-3- β -D-ribofuranosylacrylate derivative **397**, which was cyclized with aminoacetonitrile to the pyrazol-3-yl C-nucleoside **398** and then elaborated to **386** (Scheme 113).

A carefully designed synthesis of formycin was published by Buchanan and his group in Scotland and involved a *cine*-substitution of the 1,4-dinitro-

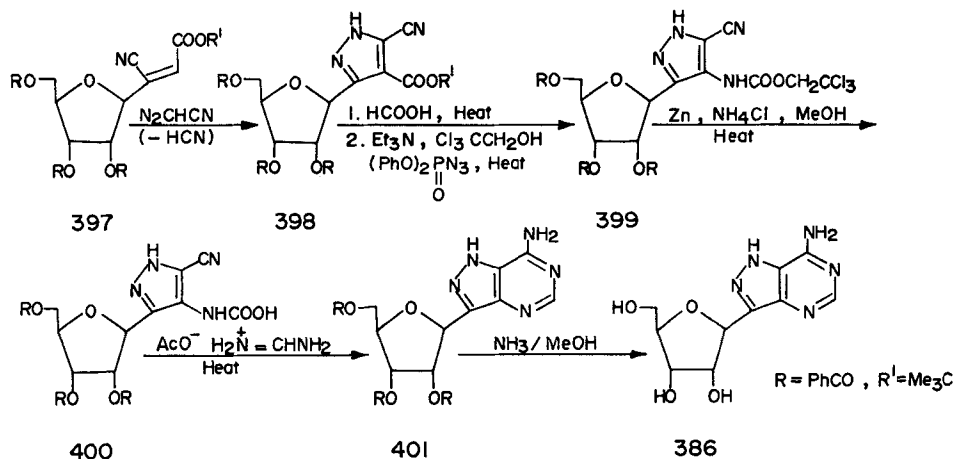


SCHEME 112

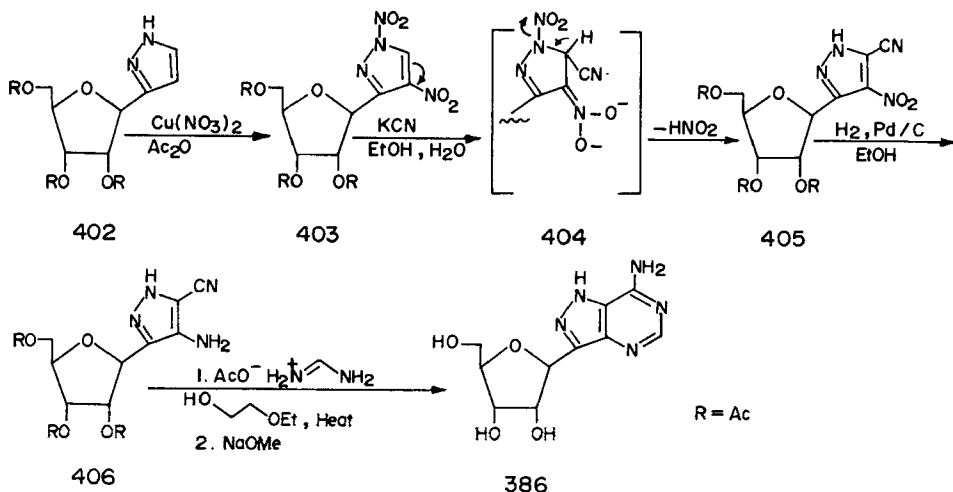
3-pyrazol-3-yl *C*-nucleoside **403** with cyanide ion to give the 3(5)cyano-4-nitro-5(3)- β -D-ribofuranosylpyrazole **405**. Catalytic reduction of **405** to the 4-amino compound **406** followed by cyclization with formamidine acetate gave formycin triacetate, which was de-*O*-acetylated to formycin **386** [80CJC2624, 80JCS(CC)237] (Scheme 114).

Formycin B (**387**) was prepared [71JCS(CC)986] from the 5-carbamoyl-4-hydrazinocarbonyl-3- β -D-ribofuranosylpyrazole **407** (70TL4611; 72CCC2798) through transformation to the 4-amino-5(3)methoxycarbonylpyrazol-3(5)-yl *C*-nucleoside **411**. Cyclization of **411** by heating with formamide and de-*O*-protection of the sugar moiety produced formycin B (**387**) (Scheme 115).

Starting with **405**, Buchanan *et al.* synthesized formycin B (**387**) by annulating the pyrimidinone ring. Compound **405** was transformed to the 4-amino-5(3)-carbamoyl-3(5)- β -D-ribofuranosylpyrazole **415** and then cyclized with formic acid and de-*O*-acetylated to **387** [84JCS(P1)2367; 84T119; 86JCS(P1)1267] (Scheme 116).

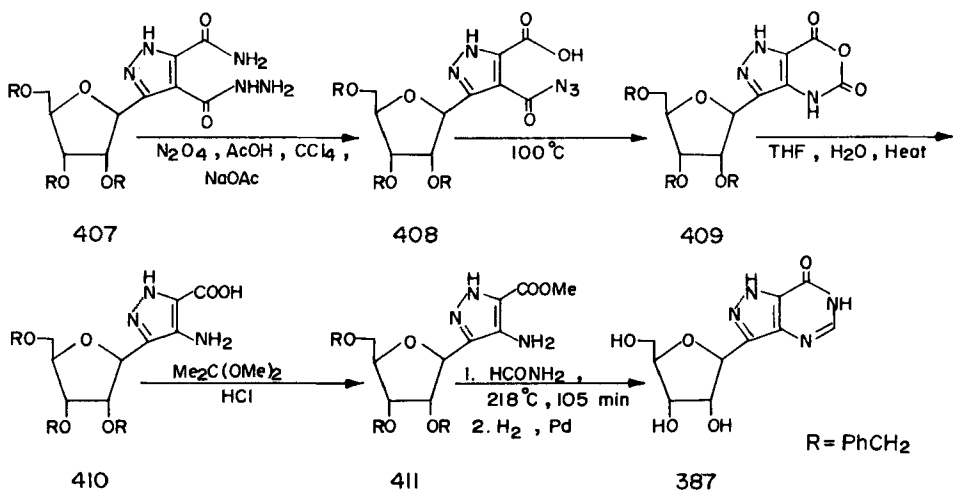


SCHEME 113

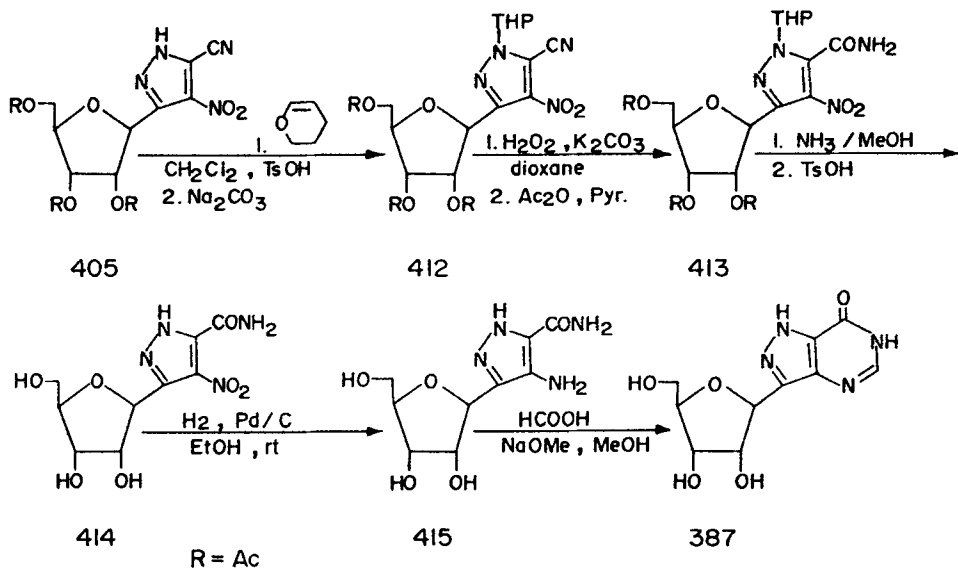


SCHEME 114

Oxoformycin B (**388**), the catabolite of formycin and formycin B, was synthesized before the parent nucleosides in 1970 from the 2,5-anhydro-1-ureido-D-allitol derivative **416**. Compound **416** was used to build the 4,5-dimethoxycarbonylpyrazol-3-yl C-nucleoside **419**, followed by construction of the fused pyrimidine ring as shown in Scheme 117. Selective amidation of the ester function at C5, rather than that at C4, is a key step during this



SCHEME 115



SCHEME 116

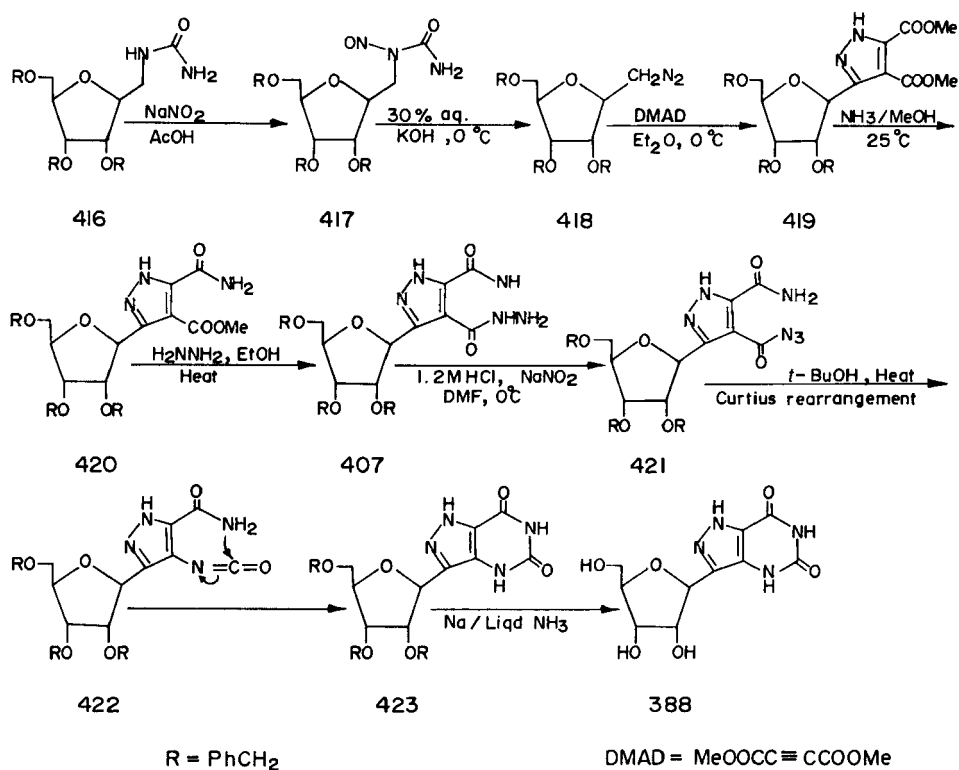
synthesis (70TL4611; 72CCC2798) (Scheme 117). The 3- β -D-arabinouranosyl congener of **388** (*ara*-oxoformycin B) was also synthesized by a similar synthetic scheme (74MI6).

Chemical deamination of formycin (**386**) with nitrosyl chloride as well as oxidation of formycin B (**387**) with bromine in water also led to the formation of oxoformycin B (**388**) (84JHC1865) (Scheme 118).

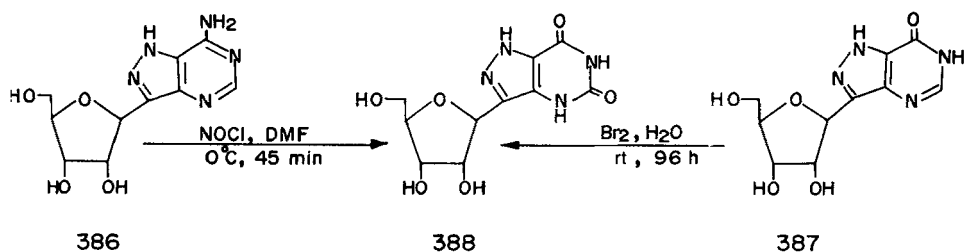
Cyclization of the 4-amino-5(3)-cyano-3(5)- β -D-ribofuranosyl-pyrazole **406** with carbon disulfide in pyridine formed dithioformycin B (**425**), most probably through the intermediate **424** (88MI7) (Scheme 119).

The pyrazolo[4,3-*d*]pyrimidinone C-nucleoside (5-aminoformycin B) **431**, a C-guanosine analog, was obtained by cyclization of the 4-amino-5(3)-carboxamidopyrazol-3(5)-yl C-nucleoside **415** as detailed in Scheme 120. The pyrazole C-nucleoside **427** was formed upon acid-catalyzed pyrimidine ring opening of formycin 6-oxide **426** (82JA1073). Alternatively, the synthesis of **431** was accomplished by transforming oxoformycin B (**388**) to the dichloro compound **432**, selective amination and deamination at C7, and amination at C5 of **433** (91MI10) (Scheme 120).

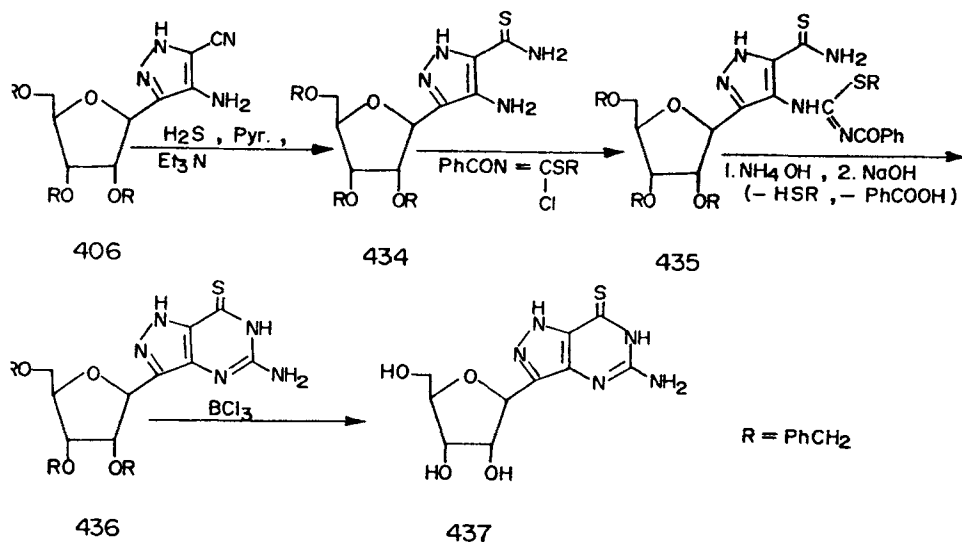
The thio analog **437** (5-aminothioformycin B) of **431** was synthesized by a similar plan from **434** as depicted in Scheme 121 (81MI1; 84JOC528).



SCHEME 117



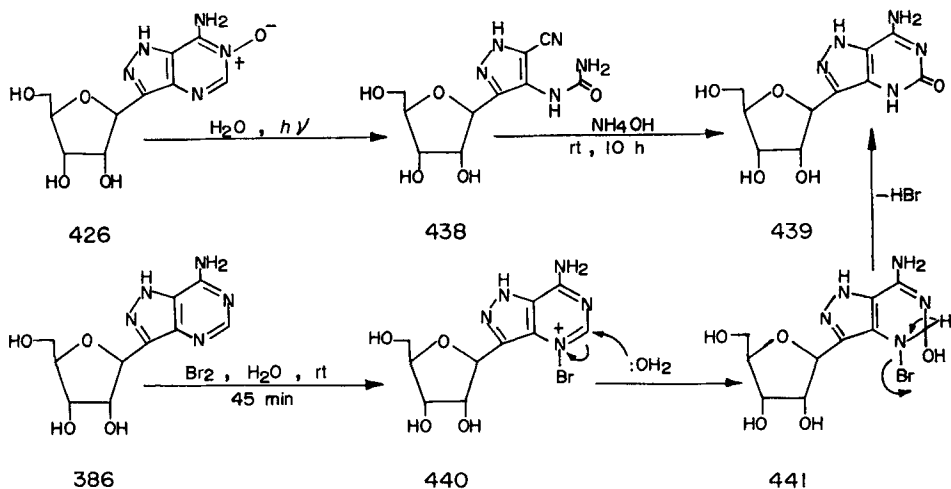
SCHEME 118



SCHEME 121

Formycin 6-oxide (**426**) was the starting substance used for the preparation of 7-amino-3-β-D-ribofuranosylpyrazolo[4,3-d]pyrimidin-5-one **439** (oxoformycin). Photo-hydrolytic pyrimidine ring opening of **426** gave the 5-cyano-4-ureidopyrazol-3-yl C-nucleoside **438**, which recycled to **439** when treated with ammonium hydroxide [84JCS(P1)2421] (Scheme 122). Another route to obtain **439** was the direct oxidation of formycin (**386**) with bromine in water; the increased double-bond character between N4 and C5 facilitated the formation of intermediate **441**, which then underwent spontaneous elimination of HBr to give **439** (84JHC1865) (Scheme 122).

The aptitude of formycin to biomimic adenosine justified the synthesis of many of its derivatives that comprised alterations in the heterocyclic and/or the sugar moieties. Studying the biological activities of the altered formycins provided valuable results concerning the structure–biological and conformation–biological activity relationships. Primarily, a suggestion has been made linking biological activities of formycin and its derivatives to their conformation: bulky groups at proper sites of the heterocyclic system cause conformational preference due to restriction of rotation about the C-glycosidic bond, a situation that affects biological activities. Special attention was directed toward the preparation of various methyl derivatives of formycin that prefer particular conformations in order to validate or refute this hypothesis. Methylation of formycin (**386**) with methyl iodide

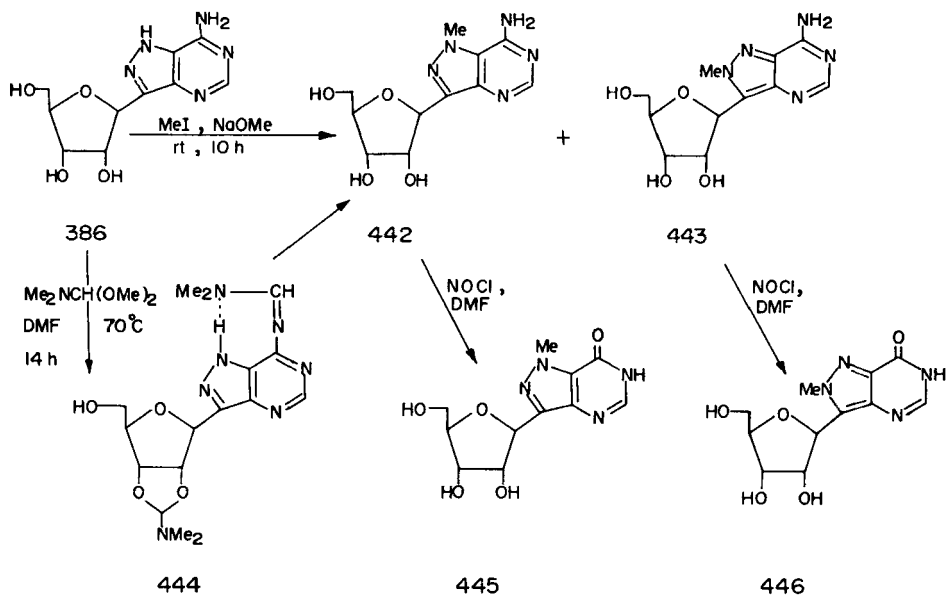


SCHEME 122

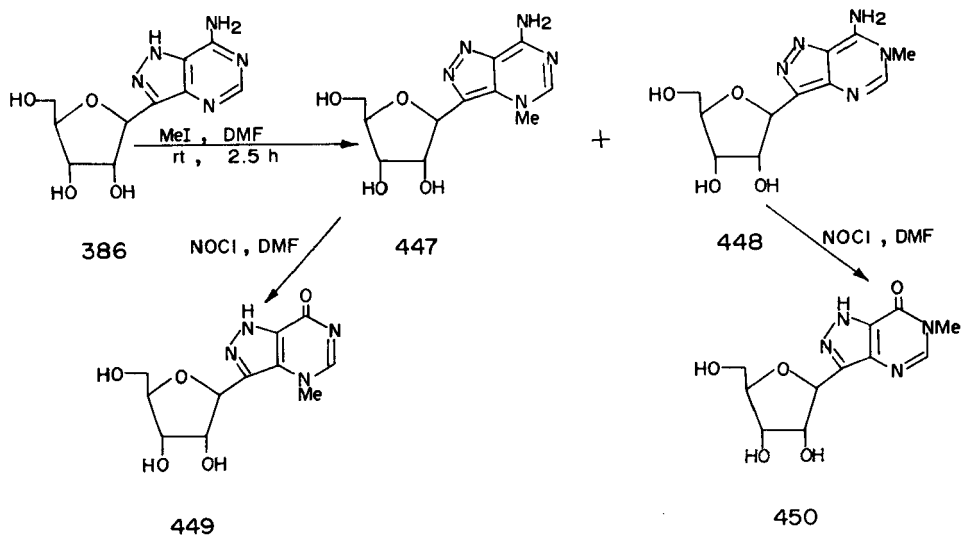
in a basic medium caused preferential methylation of the pyrazole ring and gave a mixture of 1-methyl- and 2-methylformycins (**442** and **443**) in the ratio of ~1:6, respectively (74JOC2023). Deamination of **442** (84MI12) and **443** (74JOC2023; 80JA2817) with nitrosyl chloride gave 1-methyl- and 2-methylformycin B, respectively (**445** and **446**). 1-Methylformycin (**442**) was obtained as a single product by heating formycin (**386**) with dimethylformamide dimethylacetal; the initially formed 7-(dimethylamino-methylene)amino intermediate **444** underwent intramolecular methylation to afford **442** (75JA5896; 78MI2) (Scheme 123).

Contrary to basic methylation, methylation of formycin with methyl iodide in neutral media gave a mixture of 4-methyl- and 6-methylformycins (**447** and **448**) in the ratio 2:1. Deamination of **447** and **448** afforded 4-methyl- and 6-methylformycin B **449** and **450**, respectively (80JA2817) (Scheme 124).

The pK_a measurements of the various methylformycins indicated that methylation of the pyrimidine ring nitrogens caused a significant increase in basicity, whereas methylation of the pyrazole ring nitrogens did not noticeably change the basicity as compared to that of formycin (80JA2817). Comparing the results of introducing methyl groups at the different nitrogens of formycin on biological activities such as adenosine deaminase substrate activity (74JMC62; 77MI2; 78JAN456), antiviral activity (75MI2), and antitumor activity (74JOC2023; 79MI5) invalidated the dependence of activities on conformation (*syn* or *anti*). Accordingly, electronic, steric, and/or structural parameters were considered to be the major influences on



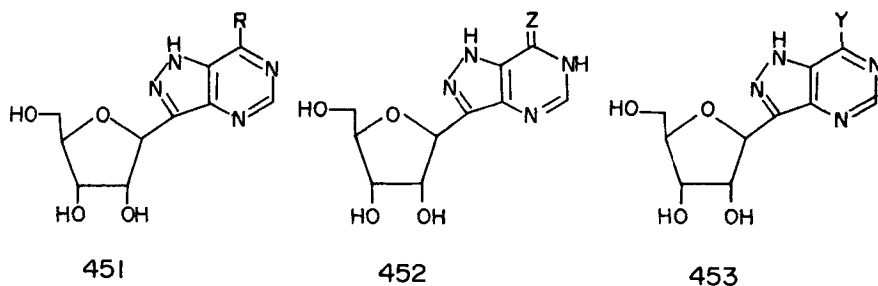
SCHEME 123



SCHEME 124

biological activities (79MI5). The methyl group at N1 of 1-methylformycin (442) was found to block binding to the adenosine deaminase active site (79MI5).

Many modifications were performed on the heterocyclic system of formycin and formycin B, which included the preparation of 451–453



$R = H, Br, I, NEt_2, NHMe, NMe_2$ $Z = S, Se$ $Y = SMe, SCH_2CH=CH_2,$

$^+NMe_3Cl^-$, $NHOH, NHNH_2, SeMe, SeCH_2Ph,$

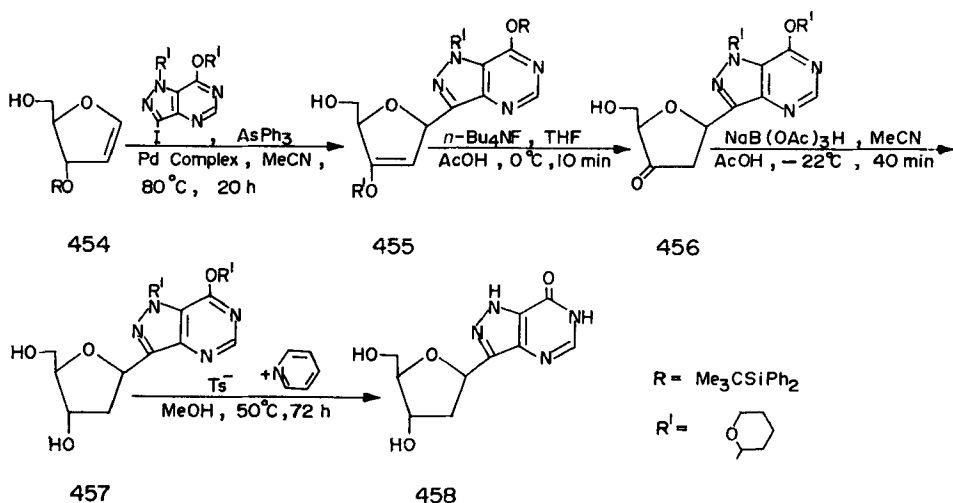
OMe

$SeCH_2C_6H_4-NO_2-p$

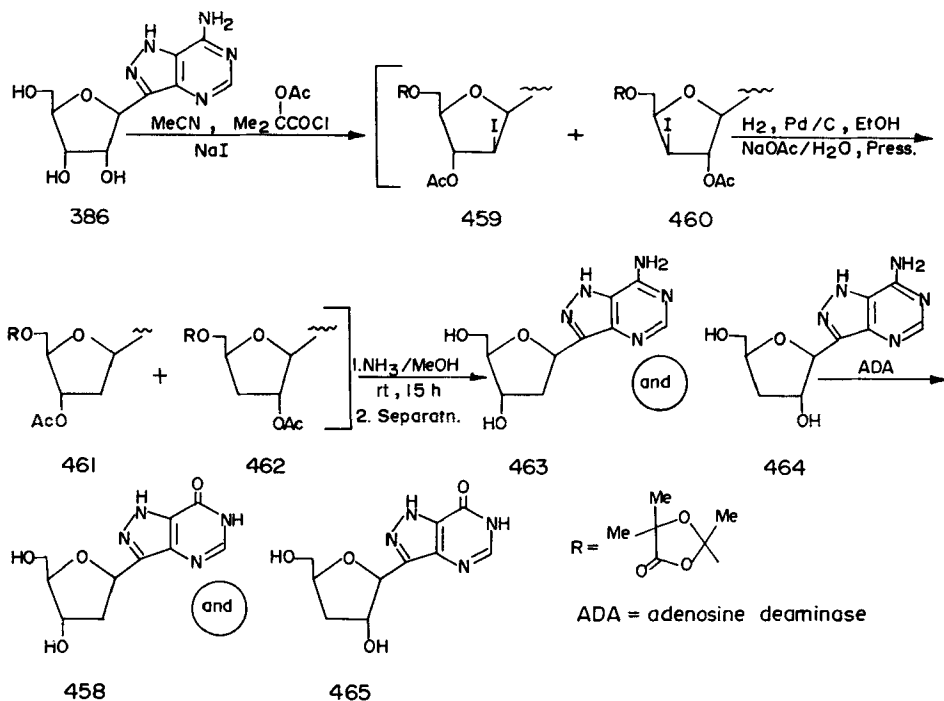
[66JAN(A)93; 72JCS(P1)2677; 82JMC1334; 85JMC1740; 86NAR1747; 95JA5951], some of which possessed antitumor (68JAN468), antibacterial [66JAN(A)93; 68JAN468] and antiviral activities [79MI2; 82JMC1334].

Formycin and formycin B with modified sugar subunits have also been prepared using, mostly, the nucleoside–nucleoside approach. In one instance, however, 2'-deoxyformycin B (458) was prepared by regio- and stereospecific palladium-mediated C–C bond formation between the furanoid glycal 454 and protected 3-iodopyrazolo[4,3-*d*]pyrimidine. The C-nucleoside 455 having an unsaturated sugar moiety was subsequently elaborated to 458 (92JOC4690) (Scheme 125).

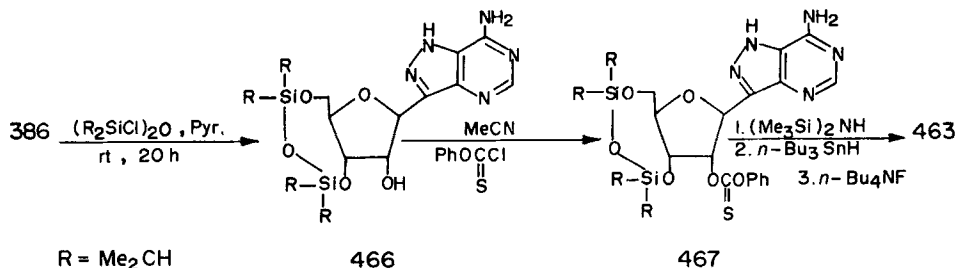
2'-Deoxy- and 3'-deoxyformycins (463 and 464) were obtained as a 2:3 separable mixture by treatment of formycin (386) with α -acetoxyisobutyryl chloride in the presence of sodium iodide. The 2'-iodo-2'-deoxy- and 3'-iodo-3'-deoxy intermediates (459 and 460) were reductively dehalogenated, de-*O*-blocked, and separated to afford 463 and 464. Enzymatic deamination of the latter with adenosine deaminase gave 2'-deoxy- and 3'-deoxyformycin B (458 and 465) (73CJC1313) (Scheme 126). The same products were also obtained with α -acetoxyisobutyryl bromide (73JOC3179; 87S879), followed by catalytic (73JOC3179) or chemical (87S879) reductive debromination of the produced 2'-bromo-2'-deoxy and 3'-bromo-3'-deoxy congeners of 459 and 460.



SCHEME 125



SCHEME 126



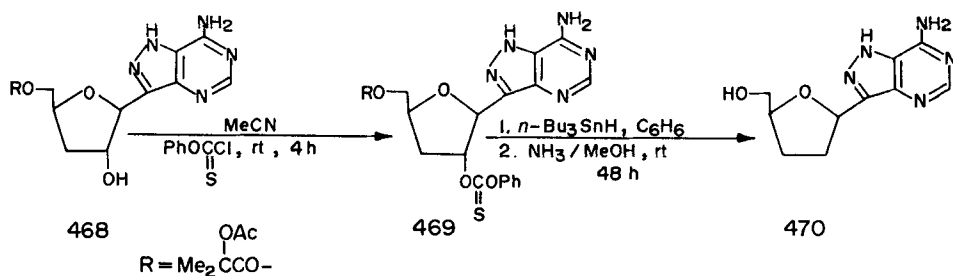
SCHEME 127

2'-Deoxyformycin (**463**) was prepared as a sole product from formycin (**386**) by protection of O3' and O5' followed by introduction and reductive removal of a 2'-O-phenoxythiocarbonyl group (85JMC1096; 89MI3) (Scheme 127). 2'-Deoxyformycin B was also prepared from formycin B according to the latter route (89MI3).

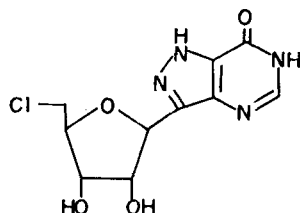
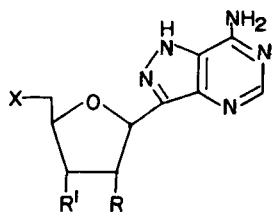
Neither 2'-deoxy- nor 3'-deoxyformycins inhibited herpes simplex type 1 virus (92JMC4576), yet 2'-deoxyformycin showed potent *in vitro* growth inhibition of S49 lymphoma cells (85JMC1096). 2'-Deoxyformycin was introduced into triplex-forming oligonucleotide sequences (92MIP1; 94MI9; 95JOC7094) useful in the treatment of HIV-1 infection (92MIP1).

2',3'-Dideoxyformycin (**470**) was synthesized by reductive removal of the 2'-O-phenoxythiocarbonyl group from the 3'-deoxyformycin derivative **469** [89BBR(161)910; 90S411]; it was found ineffective in inhibiting HIV replication [89BBR(161)910] (Scheme 128).

5'-Deoxy-5'-halogenoformycins (**471**) (86MI10; 87S879; 92JMC4576), 5'-chloro-3',5'-dideoxyformycin (**472**) (92JMC4576), 5'-chloro-2',5'-dideoxyformycin (**473**) (92JMC4576), 5'-chloro-2',3',5'-trideoxyformycin (**474**) (92JMC4576), and 5'-chloro-5'-deoxyformycin B (**475**) (86MI10) were prepared from the parent C-nucleosides by modifying their sugar residues.



SCHEME 128



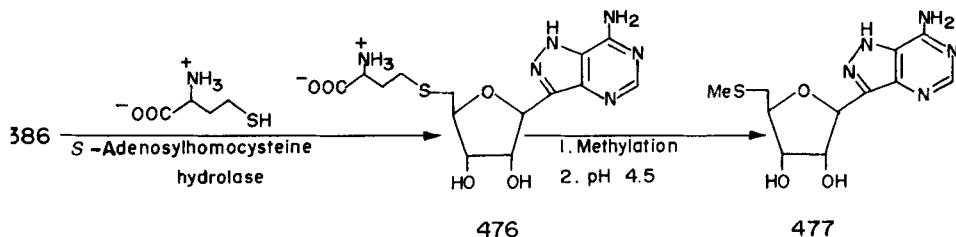
471, $R = R' = \text{OH}$; $X = \text{Br}, \text{Cl}, \text{I}$; 472, $R = \text{OH}, R' = \text{H}, X = \text{Cl}$ 475

473, $R = \text{H}, R' = \text{OH}, X = \text{Cl}$; 474, $R = R' = \text{H}, X = \text{Cl}$

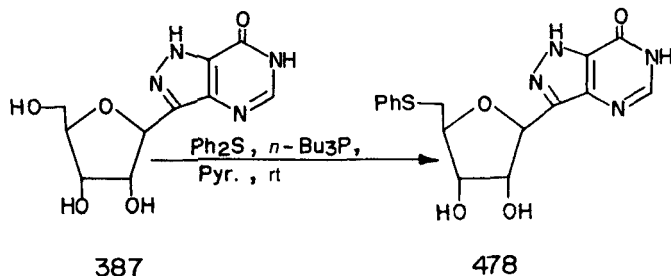
Enzymatic condensation of the thiol group of homo-L-cysteine with O5' of formycin (386) gave 476, which was *S*-methylated and subsequently hydrolyzed to 5'-deoxy-5'-methylmercaptoformycin 477. Compound 477 potentially inhibited rat liver 5'-methylthioadenosine phosphorylase (83MI4) (Scheme 129).

Reaction of formycin B (387) with diphenylsulfide and tributylphosphine took place regioselectively with the primary hydroxyl group to yield the 5'-deoxy-5'-phenylmercaptoformycin B 478 (Scheme 130). This modified C-nucleoside (478) poorly inhibited purine nucleoside phosphorylase (93JMC1024).

Modified formycins that involved both the sugar and the heterocyclic moieties include the 2,5'-anhydro- and 4,5'-anhydroformycins 481 and 484 (75JA5896, 75JAN492). These two derivatives were of particular interest because of their fixed conformation in the *anti* and *syn* forms, respectively, and their utilization to investigate the effect of conformation on enzymatic deamination by ADA. The 2,5'-anhydroformycin 481 in the *anti*-locked conformation was prepared by dehydrocyclization of 2',3'-*O*-isopropylideneformycin 479 with diethyl azodicarboxylate and triphenylphosphine (75JAN492), or by heating formycin with dimethylformamide dimethylacetal in DMF (75JA5896). The 4,5'-anhydroformycin 484 in the *syn*-locked conformation was obtained by treatment of 479 with 4-tolylsulfonyl chloride



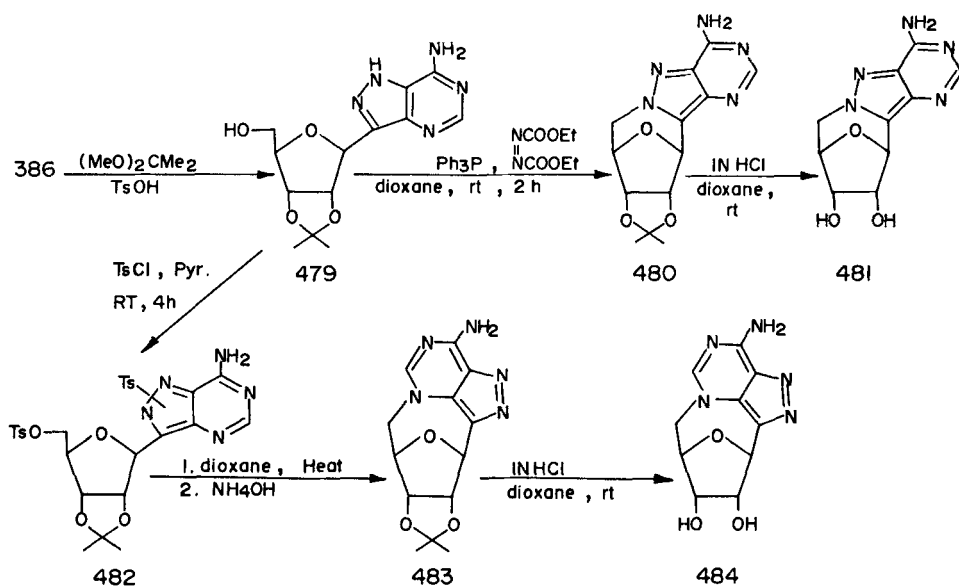
SCHEME 129



SCHEME 130

in pyridine followed by heating in dioxane (75JAN492) or with trifluoroacetic acid (75JA5896) (Scheme 131).

Similar to the parent nucleoside formycin (386), its *anti*-locked 2,5'-anhydro derivative (481) was found amenable to deamination with ADA. In contrast, the *syn*-locked 4,5'-anhydroformycin 484 resisted such deamination (75JA5896, 75JAN492). Both anhydro derivatives proved inactive against Ehrlich L1210 ascites tumors *in vivo* (75JAN492).



SCHEME 131

2. Pyrazolo[4,3-*d*]pyrimidin-5-yl C-Nucleosides

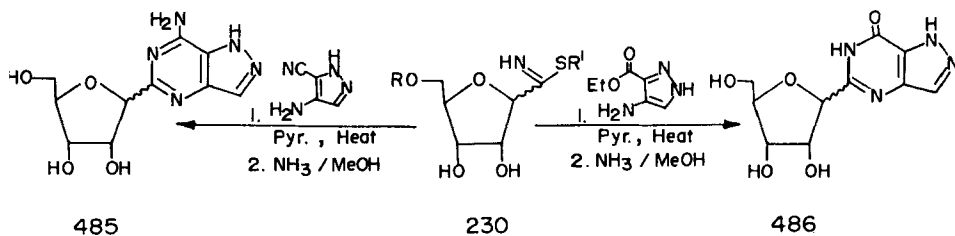
The pyrimidine rings of the pyrazolo[4,3-*d*]pyrimidin-5-yl C-nucleosides **485** and **486** were formed as a result of cyclocondensation of the β -D-ribofuranosylthioformimidate **230** with 4-amino-3-cyanopyrazole and 4-amino-3-carbamoylpyrazole, respectively. The products were obtained as a mixture of the α - and β -anomers (75JOC2825; 78NJC357) (Scheme 132). Proton spin-lattice relaxation, particularly that of the anomeric proton (H1'), proved very valuable for characterizing the two anomers of each of **485** and **486** (77JA3267).

K. PYRAZOLO[4,3-*d*]PYRIMIDINE ACYCLO C-NUCLEOSIDES

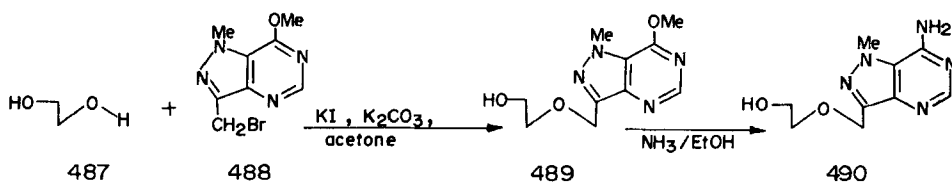
1. Pyrazolo[4,3-*d*]pyrimidin-3-yl Acyclo C-Nucleosides

The acyclo analog of 1-methylformycin **490** was prepared by etherification of 1-methyl-3-bromomethyl-7-methoxypyrazolo[4,3-*d*]pyrimidine (**488**) with ethylene glycol (**487**) and amination of the produced **489** (84JHC505) (Scheme 133). Compound **490** was devoid of antitumor and antiviral activities (84JHC505).

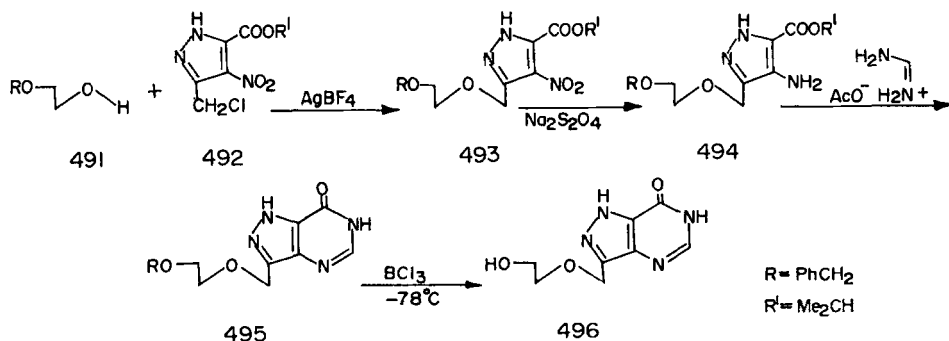
The acyclo analog of formycin B **496**, however, was synthesized by annulation of the pyrimidinone ring onto the pyrazole ring of **494**, as explained in Scheme 134. Acyclo analogs of formycin and 5-aminoformycin B were also prepared according to this approach [85JCS(P1)2087].



SCHEME 132



SCHEME 133



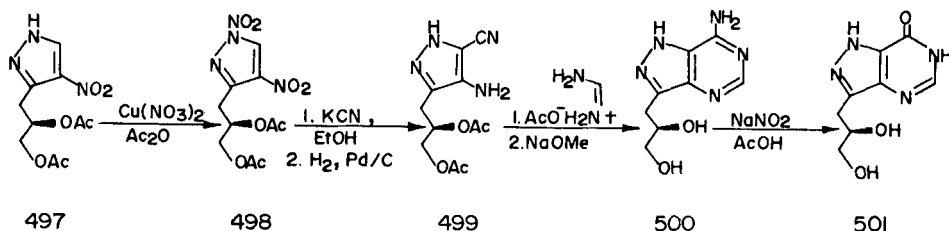
SCHEME 134

(2'*S*)-3-(2',3'-Dihydroxypropyl)pyrazolo[4,3-*d*]pyrimidines **500** and **501**, acyclo analogs of formycin and formycin B, were also synthesized by building the pyrimidine ring onto the pyrazol-3-yl acyclo *C*-nucleoside **499**. Chemical deamination of **500** gave **501** (Scheme 135). These two acyclo *C*-nucleosides did not inhibit the replication of representative DNA and RNA viruses [85JCS(P1)1425; 89JCS(P1)925].

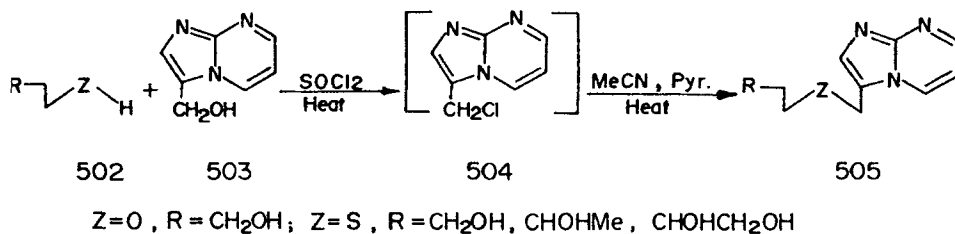
L. IMIDAZO[1,2-*a*]PYRIMIDINE ACYCLO *C*-NUCLEOSIDES

1. Imidazo[1,2-*a*]pyrimidin-3-yl Acyclo *C*-Nucleosides

The analogs of this type with truncated sugar (**505**, Z = O) and thiosugar residues (**505**, Z = S) were obtained by a one-pot etherification or thioetherification reaction of 3-hydroxymethylimidazo[1,2-*a*]pyrimidine (**503**) with the appropriate alcohol or thioalcohol (**502**) (95MI5) (Scheme 136).



SCHEME 135



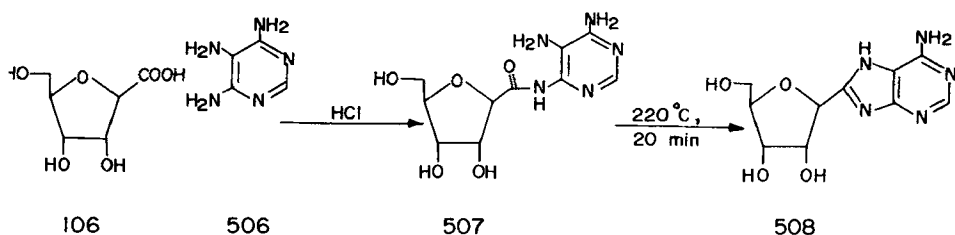
SCHEME 136

M. IMIDAZO[4,5-*d*]PYRIMIDINE C-NUCLEOSIDES

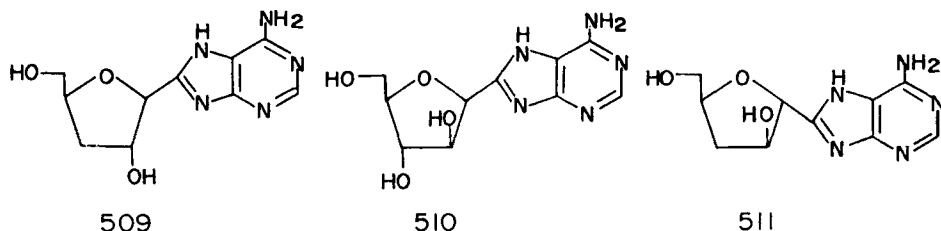
1. Imidazo[4,5-*d*]pyrimidin-2-yl C-Nucleosides

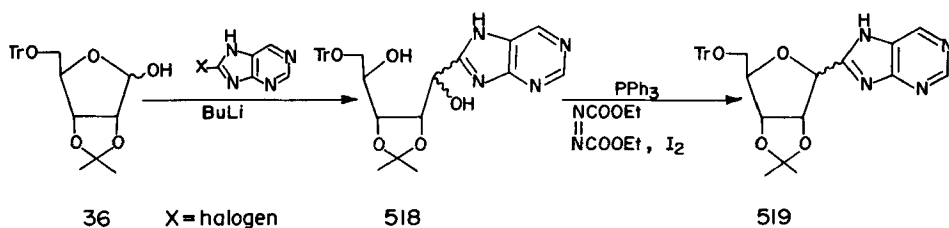
Amidation of 2,5-anhydro-D-allonic acid (**106**) with 4,5,6-triaminopyrimidine (**506**) gave the corresponding amide **507**, which then thermally cyclodehydrated to 7-amino-2-β-D-ribofuranosylimidazo[4,5-*d*]pyrimidine (8-β-D-ribofuranosyladenine or C-adenine) (**508**) (69CCC247) (Scheme 137).

The 3'-deoxy-β-D-ribofuranosyl- (cordycepin-*C*) (73MI3; 74MI5), β-D-arabinofuranosyl- (74MI4), and 3'-deoxy-α-D-xylofuranosyl- (75JMC438) analogs (**509**, **510**, and **511**) of C-adenine (**508**) were similarly prepared from the corresponding 2,5-anhydro-aldonic acid. The three C-nucleosides **509–511** were tested against blood schizontocidal malaria and found inactive (75JMC438).



SCHEME 137



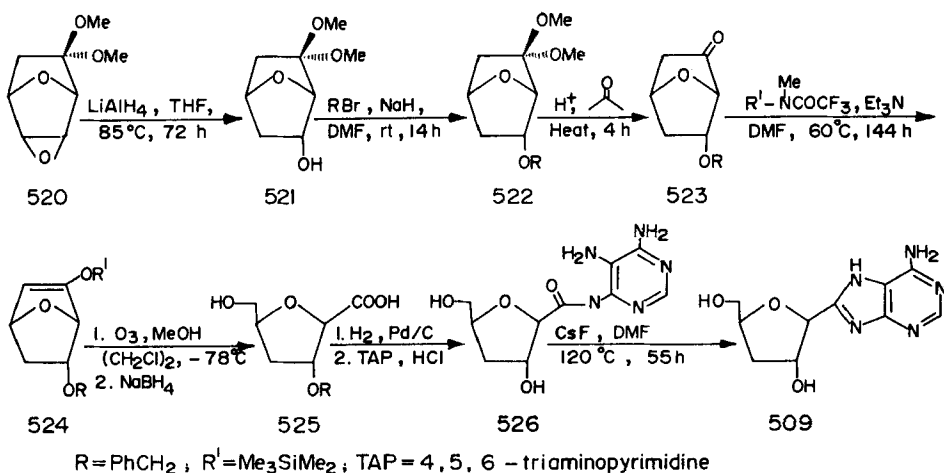


SCHEME 140

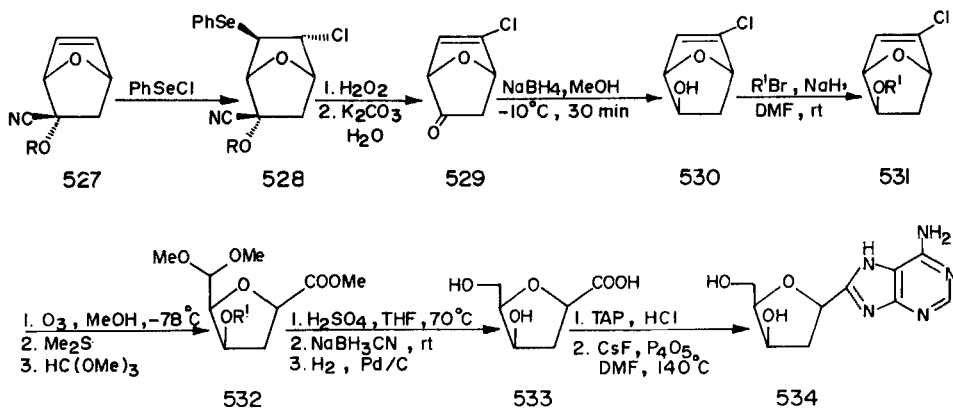
90JOC2451; 92SL676, 92T10637). Thus, the total synthesis of cordycepin-*C* (**509**) was achieved by multistep transformation of 5,6-*exo*-epoxy-7-oxabicyclo[2.2.1] heptan-2-one (**520**) to 3'-deoxy-2,5-anhydroallonic acid (**525**) and then to **509** (89HCA271). The high regioselective reduction of **520** to **521** was attributed to steric hindrance of the *endo*-methoxyl group at C2 in **520**, which impedes the competitive attack of the hydride agent onto the C5 *endo*-position. This synthesis included also the key step of employing cesium fluoride in DMF to induce smooth cyclodehydration of amide **526** at a moderate temperature without causing anomerization or thermal decomposition (89HCA271) (Scheme 141).

7-Amino-2-(2'-deoxy- β -D-xylofuranosyl)imidazo[4,5-*d*]pyrimidine (**534**) was synthesized from the 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivative **527** as outlined in Scheme 142 (90JOC2451).

Fluoro and azido substituents in the sugar moieties of nucleosides are known to amplify biological activities. Consequently, the 2-(2'-fluoro- and



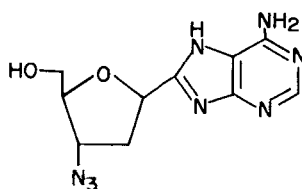
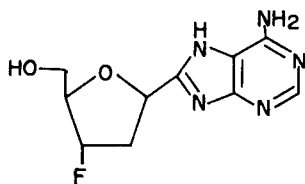
SCHEME 141



R = (1R)-Camphanoyl ; R¹ = PhCH₂ ; TAP = 4,5,6-triaminopyrimidine

SCHEME 142

2'-azido-2',3'-dideoxy- β -D-ribofuranosyl)imidazo[4,5-*d*]pyrimidines **535** and **536** were synthesized by the total synthetic approach in a plan closely similar to that used for the synthesis of **534** (92SL676, 92T10637).



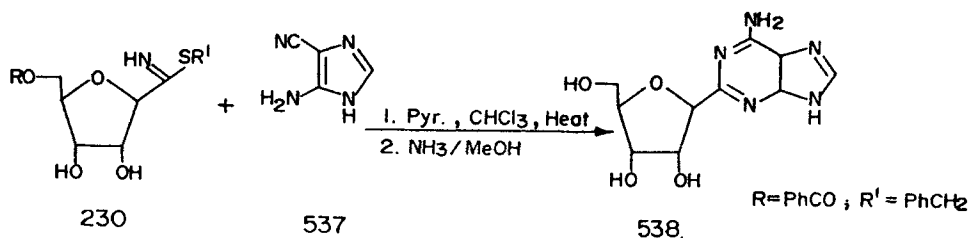
2. Imidazo[4,5-*d*]pyrimidin-5-yl C-Nucleosides

The C-nucleoside **538** pertaining to this class was obtained by condensation of the thioformimide **230** with 5-amino-4-cyanoimidazole (**537**) (75JHC111) (Scheme 143).

N. IMIDAZO[4,5-*d*]PYRIMIDINE ACYCLO C-NUCLEOSIDES

1. Imidazo[4,5-*d*]pyrimidin-2-yl Acyclo C-Nucleosides

Aldonic acids (**110**) reacted with 4,5-diamino-1,3-dimethyluracil to give the corresponding 2-(alditol-1-yl)-imidazo[4,5-*d*]pyrimidines (**539**, R = H)

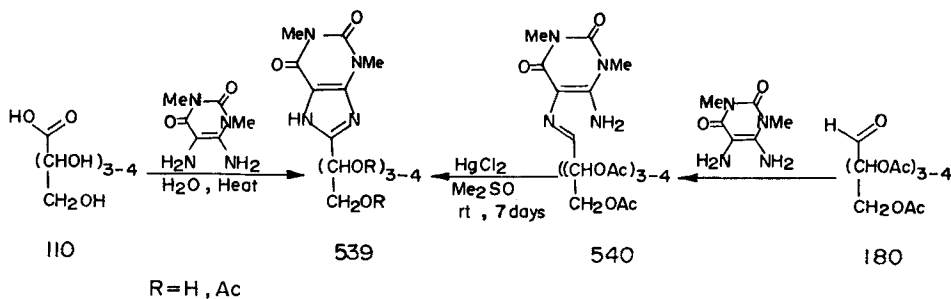


SCHEME 143

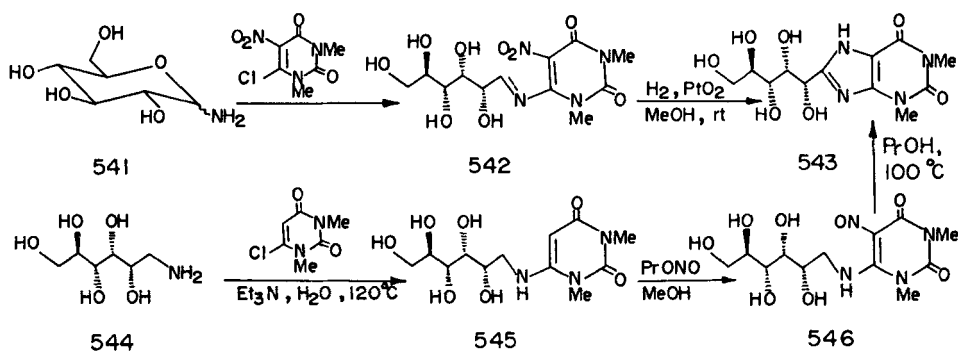
(56MI1; 74MI7). The acetates of these acyclo *C*-nucleosides (**539**, R = Ac) were obtained by oxidative cyclization of the Schiff bases **540**, derived from *aldehydo*-sugar acetates **180** and 4,5-diimino-1,3-dimethyluracil, with mercury(II) chloride in dimethyl sulfoxide [79CPB1094, 79H(12)359] (Scheme 144).

Imidazole ring formation of acyclo *C*-nucleoside **543** was made by reaction of 6-chloro-1,3-dimethyl-5-nitrouracil with *D*-glucopyranosylamine (**541**), followed by catalytic hydrogenation and concomitant cyclization of **542** (67CB492). The same *C*-nucleoside (**543**) was obtained by reacting 1-amino-1-deoxy-*D*-glucitol (**544**) with 6-chloro-1,3-dimethyluracil and subsequent nitrosation and cyclization (96S459) (Scheme 145).

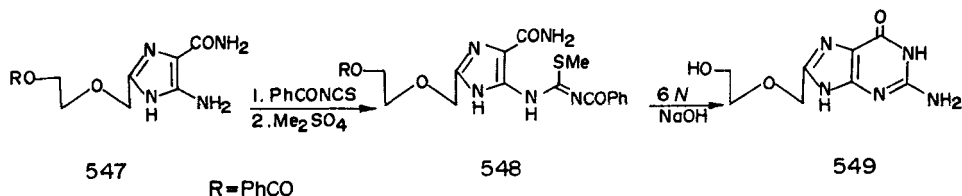
The *C*-analog **549** of the potent antiviral agent acyclovir [9-(2-hydroxyethoxymethyl)guanine (ACV)] was prepared by cyclizing the imidazol-2-yl acyclo *C*-nucleoside **547** with benzoylisothiocyanate as shown in Scheme 146 (83JHC1169).



SCHEME 144



SCHEME 145



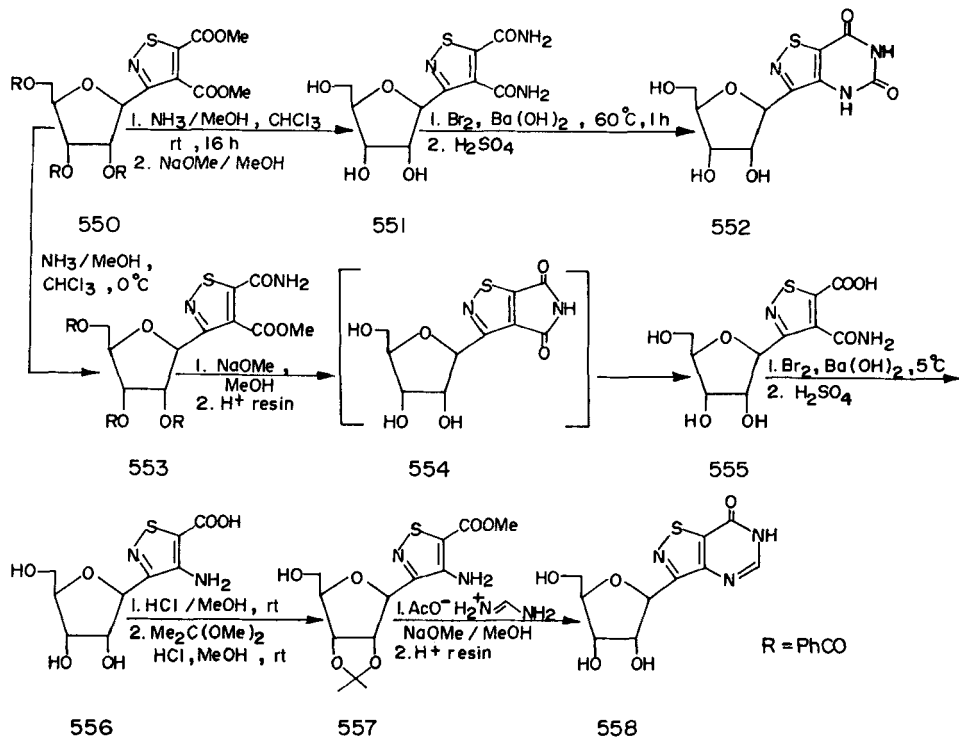
SCHEME 146

O. ISOTHIAZOLO[4,5-*d*]PYRIMIDINE C-NUCLEOSIDES

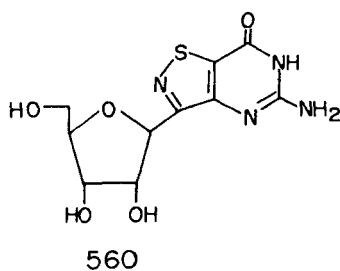
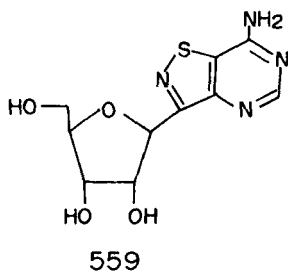
1. Isothiazolo[4,5-*d*]pyrimidin-3-yl C-Nucleosides

C-Nucleosides **552** and **558**, the analogs of oxoformycin B and formycin B, were prepared from the isothiazol-3-yl C-nucleoside **550** as explained in Scheme 147 (93JOC5181; 94MI10). This scheme comprised two key steps: (i) the selective amidation of **550** at the more reactive C5 ester group to afford **553** as a result of proximity to the ring nitrogen, and (ii) transposition of the C5 amide in **553** to C4 in **555** through the cyclic imide intermediate **554** (94MI10).

The isothiazolo[4,5-*d*]pyrimidin-3-yl C-nucleoside analogs of adenine and guanosine, **559** and **560**, respectively, were also synthesized (94JOC1912). C-Nucleosides **552**, **558**, **559**, and **560** were tested for antiviral activity against HIV, HCMV, HSV, and rhinoviruses and found inactive (93JOC5181; 94JOC1912).



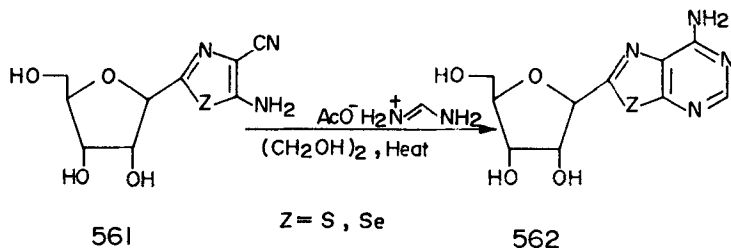
SCHEME 147



P. THIAZOLO- AND SELENAZOLO[5,4-d]PYRIMIDINE C-NUCLEOSIDES

1. Thiazolo and Selenazolo[5,4-d]pyrimidin-2-yl C-Nucleosides

Cyclocondensation of the thiazol-2-yl and selenazol-2-yl C-nucleosides **561** (R = S and Se) with formimidine acetate gave **562** (R = S and Se).



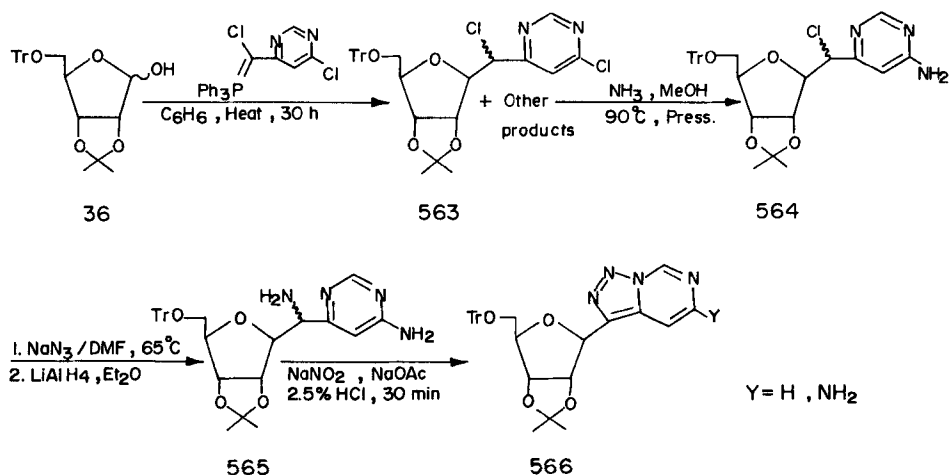
SCHEME 148

These compounds are inferior to pyrazofurin [97AHC(68)223] as antitumor agents against P388 and L1210 leukemia cells or Lewis lung carcinoma (85JOC1741) (Scheme 148).

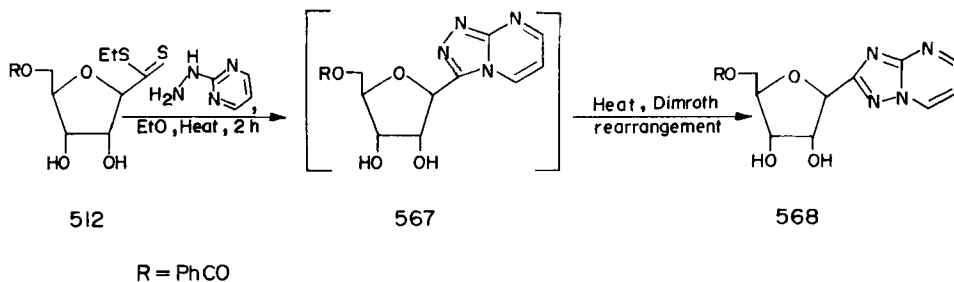
Q. 1,2,3-TRIAZOLO[1,5-*c*]PYRIMIDINE *C*-NUCLEOSIDES

1. 1,2,3-Triazolo[1,5-*c*]pyrimidin-3-yl *C*-Nucleosides

The chlorine atom of the pyrimidin-3-yl homo *C*-nucleoside **564** was displaced by azide ions followed by reduction of the introduced azido function to the amino compound **565**. Treatment of the latter with nitrous acid formed the 1,2,3-triazole ring of the two 1,2,3-triazolo[1,5-*c*]pyrimidin-3-yl *C*-nucleosides **566** ($\text{R} = \text{NH}_2$ and H) [89JCS(P1)2401] (Scheme 149).



SCHEME 149



SCHEME 150

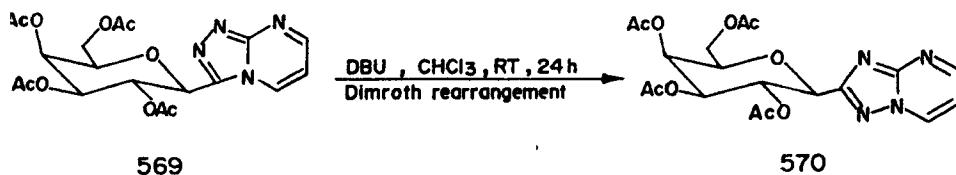
R. 1,2,4-TRIAZOLO[1,5-*a*]PYRIMIDINE C-NUCLEOSIDES1. 1,2,4-Triazolo[1,5-*a*]pyrimidin-2-yl C-Nucleosides

2,5-Anhydro-D-allonodithioate (**512**) reacted with 2-hydrazinopyrimidine to form the 1,2,4-triazolo[4,3-*a*]pyrimidin-3-yl C-nucleoside **567** as an intermediate that underwent thermally induced Dimroth-like rearrangement to the 1,2,4-triazolo[1,5-*a*]pyrimidin-2-yl C-nucleoside **568** (89MI5) (Scheme 150).

Based-induced Dimroth rearrangement of the 3-(β-D-galactopyranosyl)-1,2,4-triazolo[4,3-*a*]pyrimidine **569** (Section XI,V) also gave the corresponding 1,2,4-triazolo[1,5-*a*]pyrimidin-2-yl pyranose C-nucleoside **570** (94MI5) (Scheme 151).

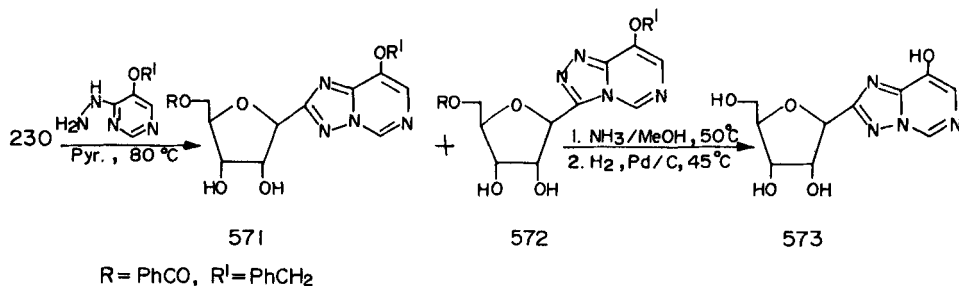
S. 1,2,4-TRIAZOLO[1,5-*c*]PYRIMIDINE C-NUCLEOSIDES1. 1,2,4-Triazolo[1,5-*c*]pyrimidin-2-yl C-Nucleosides

β-D-Ribofuranosylthioformimide (**230**) condensed with 5-benzyloxy-4-hydrazinopyrimidine to give a mixture of the 1,2,4-triazolo[1,5-*c*]pyrimidin-2-yl (**571**) and 1,2,4-triazolo[4,3-*c*]pyrimidin-3-yl (**572**) C-nucleosides in the



DBU = Diazabicyclo [5.4.0] undec-5-ene

SCHEME 151



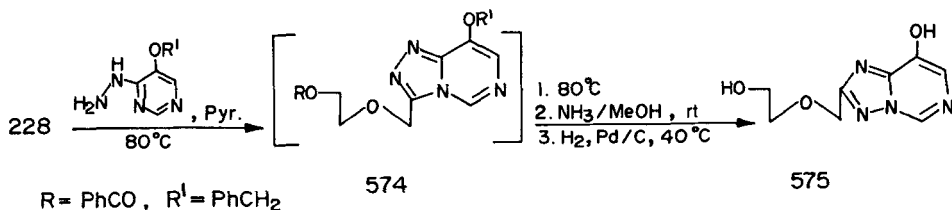
SCHEME 152

ratio 3:2. De-*O*-benzylation of this mixture with methanolic ammonia followed by de-*O*-benzylation gave only the free 1,2,4-triazolo[1,5-*c*]pyrimidin-2-yl *C*-nucleoside **573** as a result of direct deprotection of **571** as well as deprotection and base-induced Dimroth rearrangement of **572** (89JHC991) (Scheme 152).

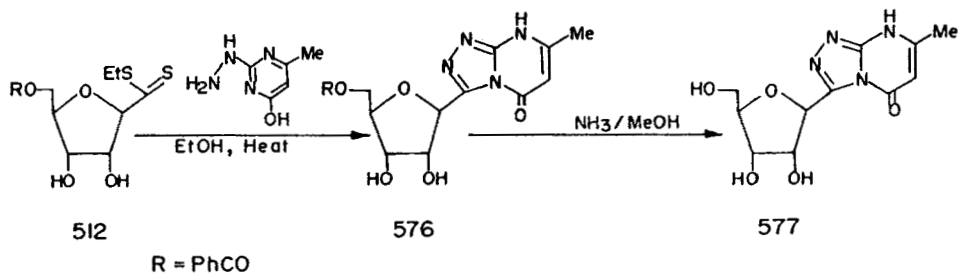
T. 1,2,4-TRIAZOLO[1,5-*c*]PYRIMIDINE ACYCLO *C*-NUCLEOSIDES

1. 1,2,4-Triazolo[1,5-*c*]pyrimidin-2-yl Acyclo *C*-Nucleosides

Acyclo *C*-nucleoside **575** was prepared in a similar way to the cyclic analog **573** by reacting 2-[2-(benzyloxy)-ethoxy]thioacetimidate **228** with 5-benzyloxy-4-hydrazino-pyrimidine. Evidently, the first-formed 1,2,4-triazolo[4,3-*c*]pyrimidin-3-yl product **574** isomerized to **575** (89JHC991) (Scheme 153).



SCHEME 153



SCHEME 154

U. 1,2,4-TRIAZOLO[4,3-*a*]PYRIMIDINE C-NUCLEOSIDES

1. 1,2,4-Triazolo[4,3-*a*]pyrimidin-3-yl C-Nucleosides

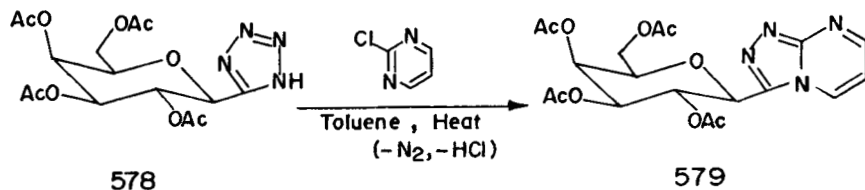
The condensed 1,2,4-triazole ring of **577** was formed as a result of condensing the β -D-ribofuranosylcarbodithioate **512** with 2-hydrazino-4-hydroxy-6-methylpyrimidine. Unlike the 1,2,4-triazolo[1,5-*c*]pyrimidine analog **568**, the 1,2,4-triazolo[4,3-*a*]pyrimidin-3-yl C-nucleoside **577** did not undergo Dimroth rearrangement (89MI5) (Scheme 154).

Heating 5-(tetra-*O*-acetyl- β -D-galactopyranosyl)tetrazole (**578**) with 2-chloropyrimidine resulted in the formation of **579** (94MI5) (Scheme 155).

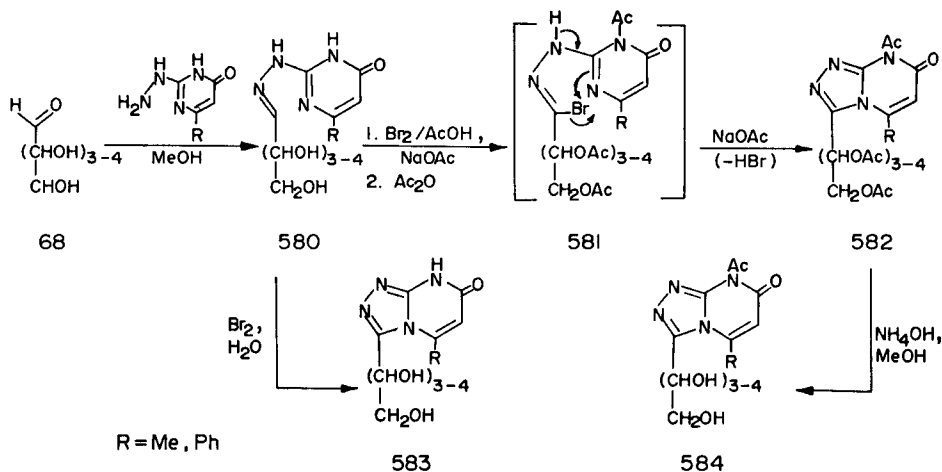
V. 1,2,4-TRIAZOLO[4,3-*a*]PYRIMIDINE ACYCLO C-NUCLEOSIDES

1. 1,2,4-Triazolo[4,3-*a*]pyrimidin-3-yl Acyclo C-Nucleosides

aldehydo-Sugar pyrimidin-2-ylhydrazones (**580**) were oxidatively cyclized and simultaneously *O*-acetylated in one-pot preparations by treatment with bromine–acetic acid–sodium acetate followed by acetic anhydride to give the poly-*O*-acetylated 8-acetyl-3-(alditol-1-yl)-1,2,4-triazolo[4,3-*a*]pyrimidin-7-ones **582**. De-*O*-acetylation of **582** gave products **584**. Cycliza-



SCHEME 155



SCHEME 156

tion of hydrazones **580** has also been performed with bromine in water to give **583**. The mass spectral fragmentation pattern of **582** indicated that cyclization took place with N1 rather N3 of the pyrimidine ring (95PHA784) (Scheme 156).

W. QUINAZOLINE C-NUCLEOSIDES

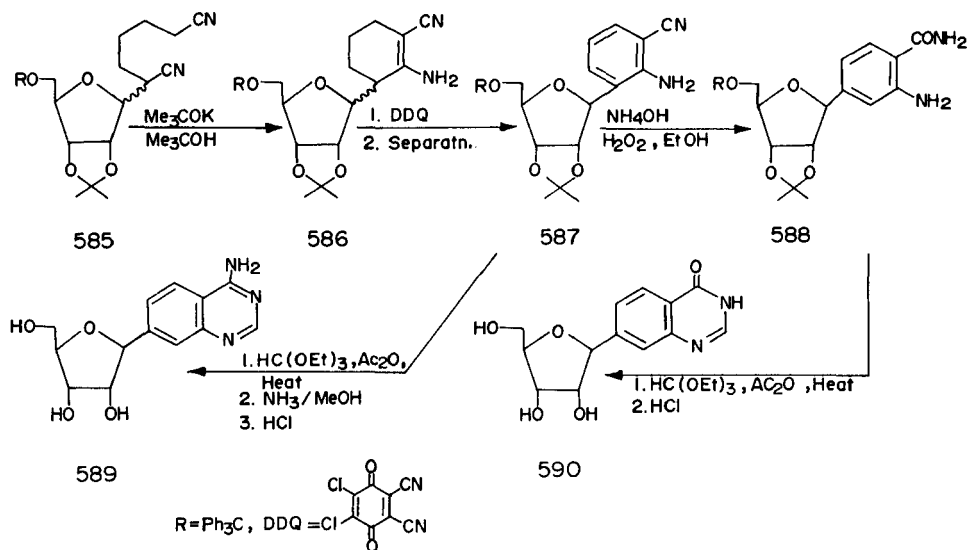
1. Quinazolin-8-yl C-Nucleosides

Annulation of a pyrimidine ring onto the β -D-ribofuranosylanthranilic acid nitrile **587** or the β -D-ribofuranosylanthranilamide **588** C-glycosides by heating with triethyl orthoformate and de-O-blocking of the protective groups on the sugar moieties provided the quinazolin-8-yl C-nucleosides **589** and **590**, respectively (95MI4) (Scheme 157).

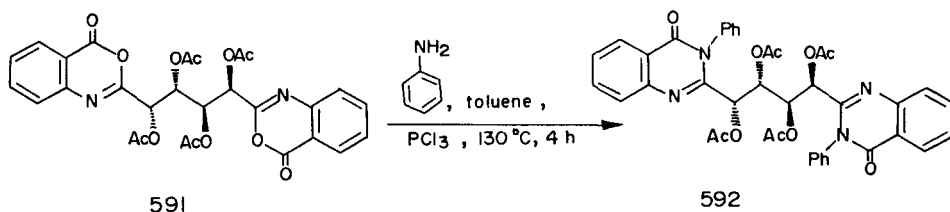
X. QUINAZOLINE ACYCLO C-NUCLEOSIDES

1. Quinazolin-8-yl Acyclo C-Nucleosides

Benzoxazine-quinazoline ring transformation was the approach used to prepare the double-headed quinazolin-2-yl acyclo C-nucleoside **592** from **591** (Section XIII,D; Scheme 207) by heating with aniline in the presence of phosphorus trichloride (87MI4) (Scheme 158).



SCHEME 157

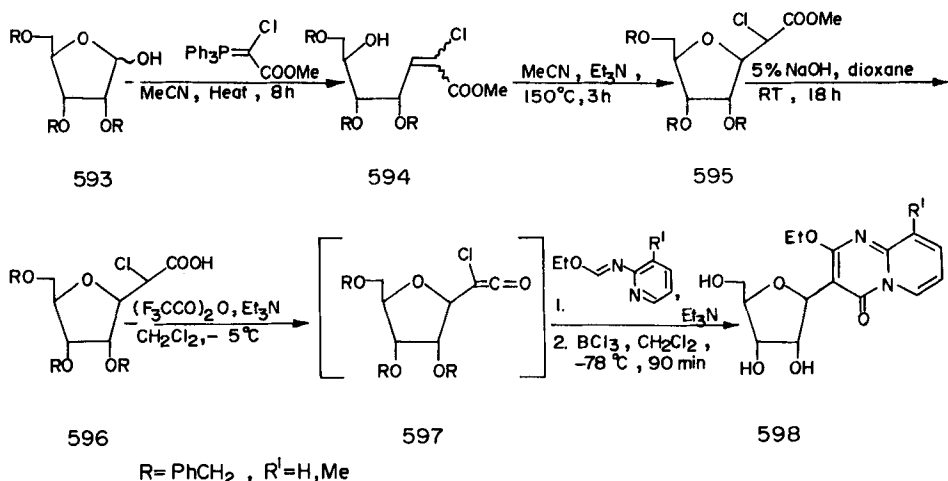


SCHEME 158

Y. PYRIDO[1,2-a]PYRIMIDINE C-NUCLEOSIDES

1. Pyrido[1,2-a]pyrimidin-3-yl C-Nucleosides

2-Alkylideneaminopyrimidines added onto the β -D-ribofuranosyl chloro-ketene **597** to give an adduct that eliminated a hydrogen chloride molecule to furnish, after de-O-protection, the pyrido[1,2-a]pyrimidin-3-yl C-nucleoside **598** (84MI3; 85CPB2671) (Scheme 159).



SCHEME 159

Z. PYRIDO[4,3-*d*]PYRIMIDINE *C*-NUCLEOSIDES

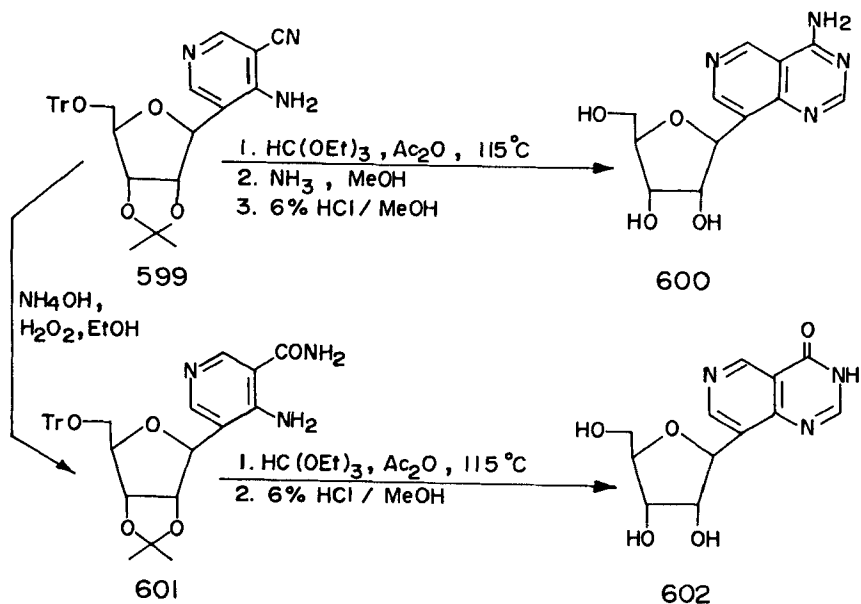
1. *Pyrido*[4,3-*d*]pyrimidin-3-yl *C*-Nucleosides

The two pyrido[4,3-*d*]pyrimidin-8-yl *C*-nucleosides **600** and **602**, the congeners of adenosine and inosine, respectively, were prepared by annulation of the pyrimidine ring onto 4-amino-3-cyanopyridine and 4-amino-3-carbamoylpyridine *C*-nucleoside **599** and **601**, respectively (92MI6) (Scheme 160).

A'. PYRIMIDO[4,5-*d*]PYRIMIDINE ACYCLO *C*-NUCLEOSIDES

1. *Pyrimido*[4,5-*d*]pyrimidin-2-yl *Acyclo C*-Nucleosides

The amino group of 6-amino-1,3-dimethyluracil added onto penta-*O*-acetyl-D-glucuronoyl isothiocyanate (**603**) to form the thiourea derivative **604**, which eliminated a molecule of water to yield the 2-(penta-*O*-acetyl-D-glucopentitol-1-yl)pyrimido[4,5-*d*]pyrimidine **605** (76MI3; 81CPB1832) (Scheme 161).

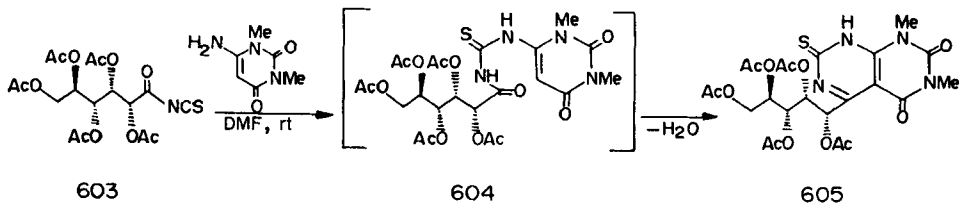


SCHEME 160

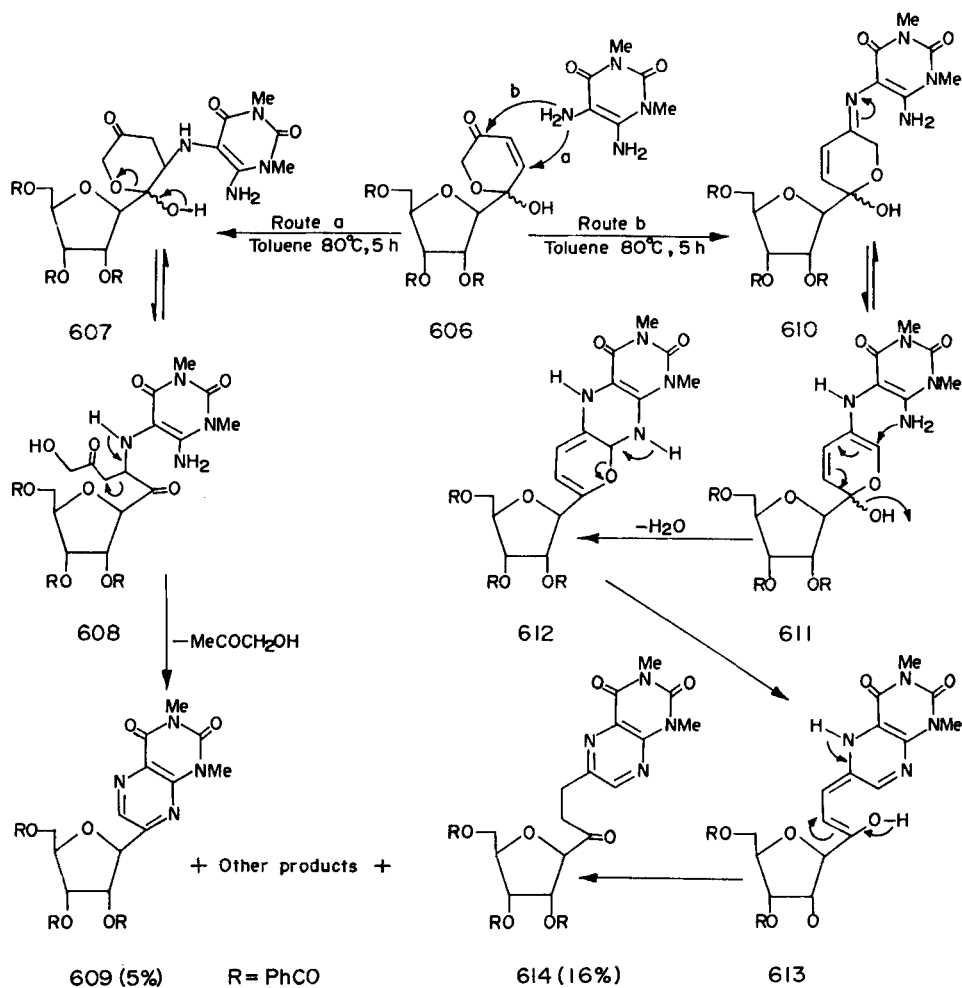
B'. PYRAZINO[2,3-d]PYRIMIDINE C-NUCLEOSIDES

1. *Pyrazino[2,3-d]pyrimidin-7-yl C-Nucleosides and Homo C-Nucleosides*

Reaction of 5,6-diamino-1,3-dimethyluracil with the 6-hydroxy-6-β-D-ribofuranosyl-2*H*-pyran-3(6*H*)-one **606** in toluene gave, in addition to another product (Section XI,Y), the lumazin-7-yl C-nucleoside (**609**) in low yield (5%) and the lumazin-7-yl homo C-nucleoside (**614**, 16%) according to the mechanisms shown in Scheme 162. When the reaction was performed in ethylene glycol, the C-nucleoside (**609**) was obtained as the main product (35%) and the homo C-nucleoside (**614**) in 13% yield (89JOC3927).



SCHEME 161



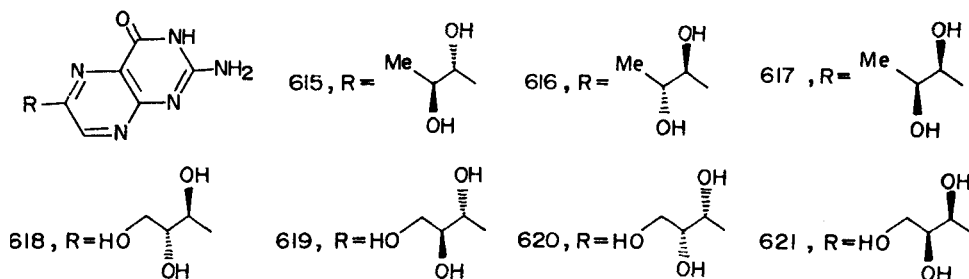
SCHEME 162

C'. PYRAZINO[2,3-*d*]PYRIMIDINE ACYCLO C-NUCLEOSIDES

1. The Naturally Occurring Pteridin-6-yl Acyclo C-Nucleosides

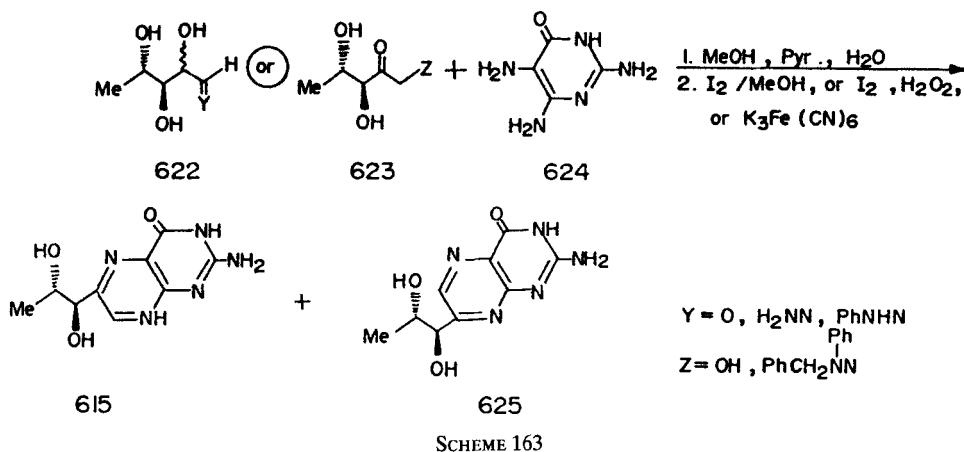
6-(Alditol-1-yl)pteridines (pteridin-6-yl C-nucleosides) are omnipresent in both the plant and animal kingdoms. They play an important role as essential cofactors for the diverse enzymes involved in biological hydroxylation processes. Extensive work has been performed toward isolation, struc-

ture elucidation, and synthesis of naturally occurring members of this class, as well as the synthesis of their congeners. Trivial names have usually been given to most of the naturally occurring members of this class, among which are biopterin (**615**), dictyopterin (**616**), orinapterin (**617**), D-neopterin (**618**), L-neopterin (**619**), D-monapterin (**620**), and L-monapterin (umanapterin) (**621**). A few of the isolated naturally occurring members, however, were systematically named.



a. *Biopterin and Related Compounds.* Biopterin [2-amino-6-(L-erythro-1',2'-dihydroxypropyl)-4-oxo(3-H)pteridine] (**615**) is widely distributed in eukaryotes and prokaryotes [63LA(662)72; 64AGE114; 72AGE1061; 75MI5; 80MI3; 82MI3; 84MI4]. Thus, it has been isolated from human urine [55JA3167; 56JA5871; 59BP814462; 72JBC(257)4549], human saliva (89MI1), reptile skins (60MI2), royal jelly of the honeybee [58ZPC(311)79], insects (*Drosophila melanogaster*) (55HCA397, 55JA4865; 77MI3), Mexican leaf frog larvae (78MI3), parasitic helminths (*Ascaris lumbricoides*) (70MI4), *Plodia interpunctella* (71MI1, 71MI2), and bacteria (*Escherichia coli*) [61BBR(6)180]. The structure of biopterin was determined by degradation (55HCA1222, 55JA4865) and mass spectral fragmentation (72TL3219). Biopterin (**615**) has frequently been synthesized, together with its 7-alditolyl isomer (primapterin, **625**), by oxidative cyclocondensation of 2,5,6-triaminopteridin-4-one (**624**) with either of the two C2 epimeric 5-deoxyl-1-aldopentoses **622** or their hydrazones [55JA4865; 56JA5868; 58HCA108; 62LA(658)193, 62ZPC(329)291; 63CB1395; 75BCJ3767; 77HCA211; 79BCJ181; 80BCJ2344; 81MI3; 85HCA1639; 89JAP(K)89/221380, 89LA 1267], as well as the 5-deoxyl-L-ribulose **623** or its hydrazones (69HCA1225; 72HCA570, 72HCA574) (Scheme 163).

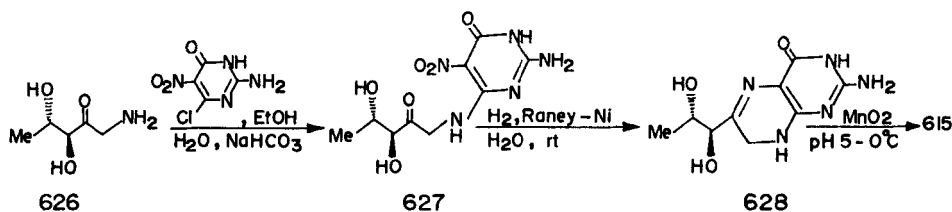
This method suffers the laborious separation of the two isomeric C-nucleosides **615** and **625** and characterization of the structure of each. To circumvent these difficulties, biopterin **615** was obtained as a sole entity by reacting 1-amino-1-deoxy-L-erythro-pentulose **626** with 2-amino-4-

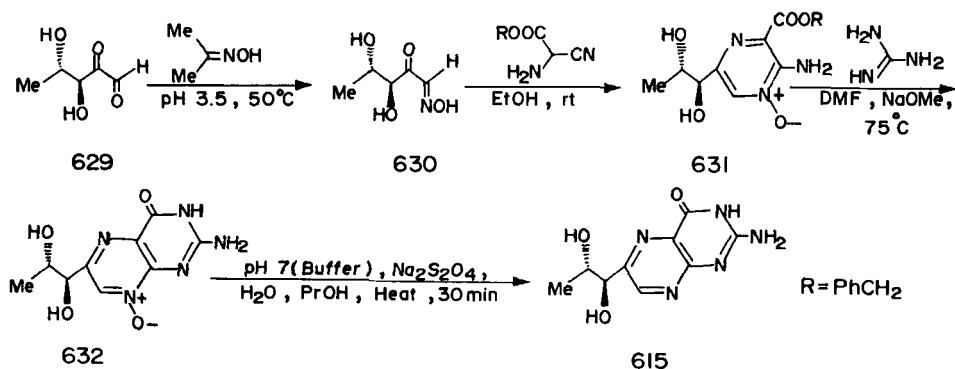


chloro-5-nitropyrimidin-4-one. The nitro group of the produced **627** was catalytically reduced and concomitantly cyclized to the 7,8-dihydrobiopterin **628**. Oxidation of **628** with manganese dioxide gave **615** [68JCS(CC)120; 69JCS(C)928; 77MI4] (Scheme 164).

Taylor and Jacobi contrived the unequivocal synthesis shown in Scheme 165 to obtain only biopterin (**615**); both of the pyrimidine and pyrazine rings were elaborated onto the alditolyl moiety during this synthesis. A key step during this synthesis was the regiospecific transoximation of the aldehyde function of 5-deoxy-*L*-erythro-pentulose **629** with acetone oxime **630** (74JA6781; 76JA2301). Synthesis of ^{13}C 8a biopterin was also accomplished according to this synthetic plan for utilization in biochemical studies (79MI7).

7,8-Dihydrobiopterin (**628**) and 5,6,7,8-tetrahydrobiopterin (**633**) are two biologically important derivatives of the parent compound (**615**). The dihydro derivative (**628**) was isolated from the skin of five different species of *Crenilarius* fishes [63ZN(B)551]. The tetrahydro derivative (**633**) was iso-



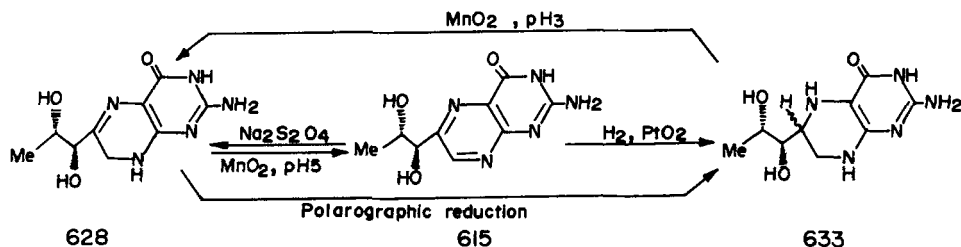


SCHEME 165

lated from the same species of fishes [63ZN(B)551] and from the cyanobacterium (blue-green alga). *Anacystis nidulans* (63MI1; 66MI2). Chemical transformation of the three derivatives to each other is explained in Scheme 166 (66MI2; 73LA1091; 78HCA2731; 79HCA2577; 81MI3; 86EP191335, 86MI6). The autooxidation of tetrahydrobiopterin was studied using ESR spectrometry [74CI(L)233].

The absolute configuration at C6 of the natural tetrahydrobiopterin was studied using NMR and CD spectroscopy (82AJC785) and X-ray crystallographic analysis (85MI5) and found to be *R*, with the alditoyl chain occupying a quasi-equatorial position.

Tetrahydrobiopterin (**633**) is an essential enzyme cofactor in a number of hydroxylation and oxygenase reactions (72AGE1061; 83MI6), including hydroxylation of phenylalanine to tyrosine (63PNA1085), tryptophan to 5-hydroxytryptophan (serotonin) [66MI1; 67SCI217; 74MI3; 80BBA(611)241; 91MI2], hydroxylation of dihydroorotic acid [73BBR(53)929], and 17 α -hydroxylation of progesterone (72MI2). It also acts as an essential cofactor in melanin synthesis [68ZN(B)860] and in the conversion of tyrosine to the neurotransmitter L-dopa (3,4-dihydroxy-L-phenylalanine) (71MI3). The



SCHEME 166

biochemical activities of the natural (6*R*)-tetrahydrobiopterin and the synthetic (6*S*)-isomer were studied; both were found active *in vitro*, but only the natural isomer was found active *in vivo* (86MI6; 88MI3). Abnormalities of biopterin and tetrahydrobiopterin metabolism are linked to the incidence of some metabolic diseases such as Parkinson's disease and phenylalaninemia (85MI4, 85MI6; 92MI5; 93MI2). Some *O*- and *N,O*-acylated derivatives of tetrahydrobiopterin were patented as useful preparations for the treatment of these diseases (83EP79574; 85USP4550109; 86EP191335; 89EP318926).

3-Methylbiopterin and 2'-deoxybiopterin are two naturally occurring pterin-6-yl acyclo *C*-nucleosides related to biopterin. The former was isolated from methanol extracts of the marine anthozoan *Asteroides calycularis* Pallas and found to inhibit growth of mouse and chick fibroblasts in culture (87E950), whereas the latter was isolated from urine of patients with malignant lymphoma (95MI2).

b. *Dictyopterins*. 2-Amino-6-(*D*-threo-1',2'-dihydroxypropyl)pteridin-4-one (dictyopterins, **616**) was isolated from the vegetative cells of the amoeba *Dictyostelium discoideum* (90MI3). It was synthesized, prior to its isolation, by the conventional method of oxidative cyclocondensation of 5-deoxy-D-xylose with 2,5,6-triaminopyrimidin-4-one (**624**) (58HCA108; 66CB2162) in a similar way to that used for the synthesis of biopterin (Section XI,C',1,a; Scheme 163).

c. *Orinapterin*. It was isolated from human urine and its structure was determined as 2-amino-6-(*L*-threo-1',2'-dihydroxypropyl)pteridin-4-one (**617**) (92ZPC1061). It was synthesized by the classical method of reacting **624** and 5-deoxy-L-xylose (66CB2162).

d. *D- and L-Neopterins*. *D*-Neopterin, 2-amino-6-(*D*-erythro-tetritol-1-yl)pteridin-4-one (**618**), and its *L*-enantiomer (**619**) were found in various natural sources, including human saliva (89MI2) and urine [67MI4; 72JBC(247)4549], ovine pineal glands (84MI2), insects [63CB1406, 63LA(662)72; 79MI6; 80MI2], Mexican frog larvae (78MI3), leguminous plants (80E639), and bacteria (69MI3; 80ABC2061).

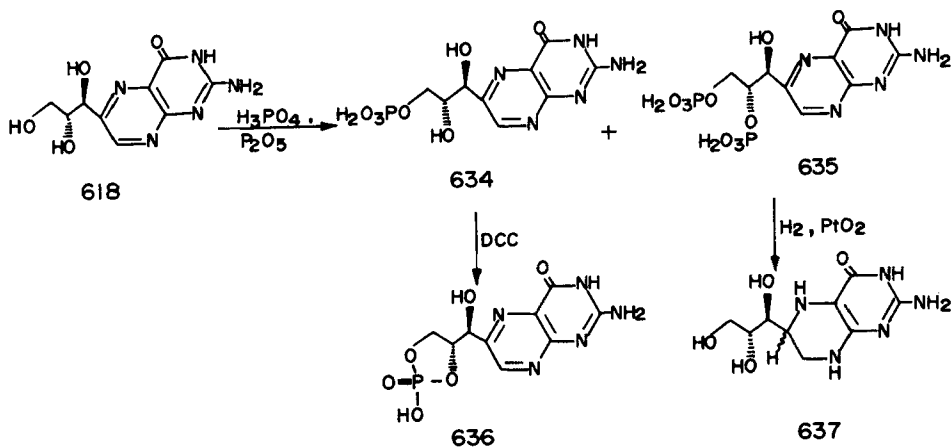
D-Neopterin (**618**) was synthetically obtained by reacting the triaminopyrimidine **624** with *D*-ribose (63CB1406), *aldehyde-D*-ribose phenylhydrazone (70HCA1202), or *aldehyde-D*-arabinose hydrazone (58JA2018) in a way similar to that described in Scheme 163. *D*-Neopterin 3'-phosphate was chemically prepared from **624** and *D*-ribose 5-phosphate (65CB851) and biosynthetically obtained from guanosine triphosphate by treatment with the cell-free extracts of *Pseudomonas* species ATCC11299a

[66JBC(241)2220] or *Serratia indica* IFO3759 (72ABC1685, 72ABC1695). A mixture of D-neopterin 3'-monophosphate (**634**) and 2',3',-diphosphate (**635**) was obtained when D-neopterin (**618**) was phosphorylated with a mixture of phosphoric acid and phosphorus pentoxide (72BCJ3564). Cyclization of the 3'-monophosphate **634** with DCC afforded the 2',3'-cyclic phosphate **636** (72BCJ3564). Catalytic hydrogenation of the diphosphate **635** gave a mixture of the (6*R*)- and (6*S*)-5,6,7,8-tetrahydro-D-neopterin **637** (86HCA210) (Scheme 167).

D-Neopterin labeled at the amino group or N3 with enzyme or fluorescent markers was prepared for utilization in immunoassays of neopterin [93GEP(D)4308739]. Dihydro-D-neopterin 3'-phosphate labeled at C1' and C2' with ^3H has also been prepared (91MI3).

L-Neopterin (**619**) was synthesized by reactions similar to those used to obtain its D-enantiomer **618** [56CB2904; 58JA2018; 68HCA1495, 68-JCS(CC)120; 69JCS(C)928]. The preparation of 5,6,7,8-tetrahydro-L-neopterin, by catalytic reduction of the parent compound (**618**) (76HCA248) and its 2-*N*-acetyl-1',2',3'-tri-*O*-acetyl-5,6,7,8-tetrahydro-L-neopterin (79HCA2558; 86HCA210) were reported.

L-Neopterin (**619**) serves as a biosynthetic precursor for biopterin, and their ratio in biological fluids is a good criterion to diagnose malignancy, gout, uremia, and liver disease (91MI2). It was found to provide protection against free-radical-induced injuries such as those encountered with adriamycin cardiotoxicity and gastric ischemic injury (94MI3). L-Neopterin and biopterin are significant in the immune system (94MI4), and 5,6-dihydro-neopterin is used as a drug for the treatment of Parkinson's disease [86JAP(K)86/29382].



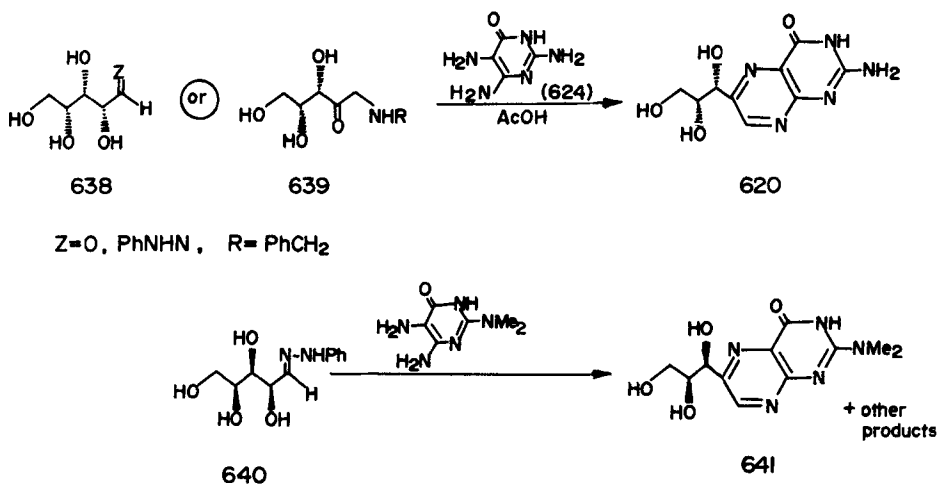
SCHEME 167

e. *D* and *L*-Monapterins. The first synthesis of 2-amino-6-(*D*-*threo*-tetritol-yl)pteridin-4-one (*D*-monapterin, **620**) was reported as early as 1947 by the reaction of *D*-xylose (**638**, $Z = O$) with 2,5,6-triaminopyrimidin-4-one (**624**) (47HCA1031; 58JA2018; 63CB1406). *D*-Xylosulose (*D*-xylosone) (51USP2541717), 1-benzylamino-1-deoxy-*D*-xylulose (**639**) (68HCA1495), and *D*-xylose phenylhydrazone (**638**, $Z = NNHPh$) (70HCA1202) also reacted with **624** to give **620** (Scheme 168). Compound **620** has been identified in the ciliate protozoan *Tetrahymena pyriformis* (92MI2).

Reaction of **620** with polyphosphoric acid produced a mixture of *D*-monapterin 3'-monophosphate and 2',3'-diphosphate (72BCJ3564).

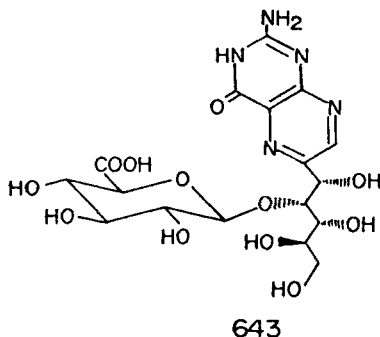
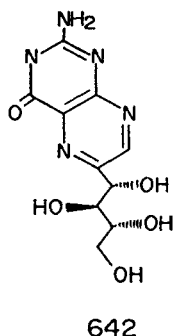
L-Monapterin (**621**) was isolated from bacteria (64HCA1948; 80N610), human urine [72JBC(247)4549], and saliva (89MI1). *L*-Monapterin (**621**) (47HCA1031; 63CB1406; 68HCA1495), its 3'-monophosphate, and its 2',3'-diphosphate (72BCJ3564) were synthesized by reactions similar to those used for the synthesis of *D*-monapterin (**620**) and its phosphates. *L*-Monapterin was biosynthesized from guanosine triphosphate by incubation with cell-free extracts of *Serratia indica* (72ABC1685, 72ABC1695).

f. *Euglenapterin*. This compound was found in the unicellular alga *Euglena gracilis*; its structure was determined as 2-dimethylamino-6-(*L*-*threo*-tetritol-1-yl)pteridin-4-one (**641**) (76MI4). It was synthesized, together with other products, from *L*-xylose phenylhydrazone (**640**, $Z = NNHPh$) and 5,6-diamino-2-dimethylaminopyrimidin-4-one (80AGE473) (Scheme 168).



SCHEME 168

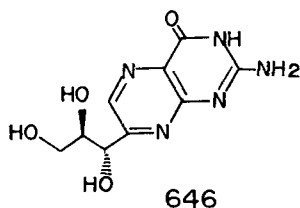
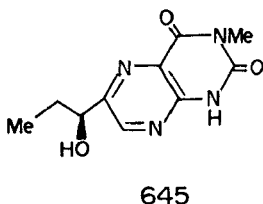
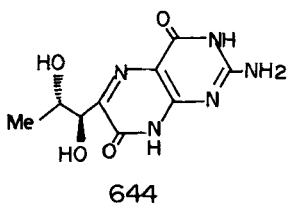
g. *2-Amino-6-(D-ribo-tetritol-1-yl)pteridin-4-one*. This pteridine acyclo C-nucleoside **642** was isolated from the bacterium *Rhodopseudomonas sphaeroides* GM-1. It has not been given a trivial name (93MI3).



h. *2-Amino-6-[2-(β-D-glucouronopyranosyl)-D-glucopentitol-1-yl]pteridin-4-one*. Isolation of this compound **643** from *Mycobacterium smegmatis*, elucidation of structure, and synthesis was reported by Goto *et al.* [65LA (689)221].

i. *Ichthyopterin*. Ichthyopterin has the structure of 2-amino-(L-erythro-1',2'-dihydroxypropyl)pteridin-4,7-dione (**644**) (91MI4) and was isolated from the skin of goldfish [43LA(554)69; 59LA(625)133] and scales of the cyprinid fish *Misgurnus anguillicaudatus* (55MI1; 68MI5).

j. *Leucettidine*. Leucettidine is a naturally occurring pteridin-6-yl acyclo C-nucleoside that was isolated from extracts of the calcareous sponge *Leucetta microraphis*. Its structure, which was found to be 6-[(1'S)-1'-hydroxypropyl]-3-methylpteridine-2,4-dione (**645**), represents a deviation from the usual substitution pattern of these compounds in having a mono-oxygenated propyl group and no amino group at C2 (81JOC4782).



2. *The Naturally Occurring Pteridin-7-yl Acyclo C-Nucleosides "Primapterin" and "Anapterin"*

Primapterin [2-amino-7-(*L*-erythro-1',2'-dihydroxypropyl)pteridin-4-one] (**625**) and anapterin [2-amino-7-(*D*-erythro-1',2',3'-trihydroxypropyl)pteridin-4-one] (**646**) are the two naturally occurring pteridin-7-yl acyclo C-nucleosides known thus far.

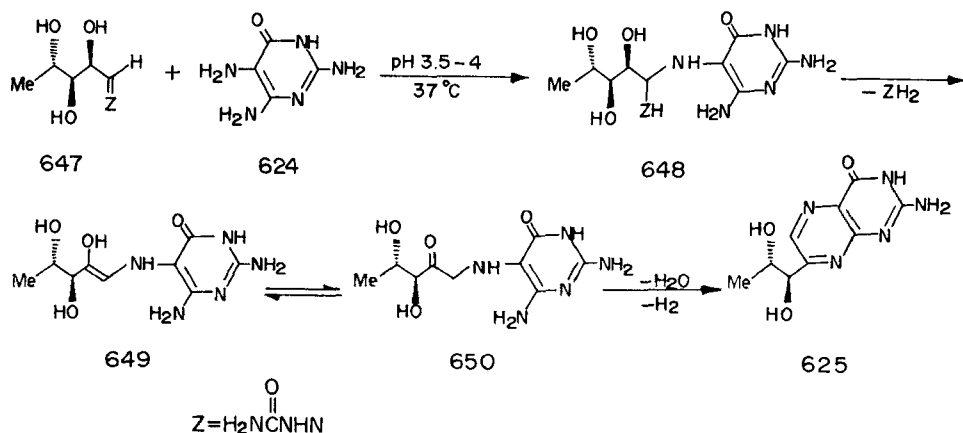
Both **625** and **646** were isolated from urine of patients with a transient type of hyperphenylalaninemia that is related to a bipterin synthetase deficiency [88BBR(153)715, 88MI4, 88MI5; 90HCA1064]. Anapterin (**646**) was also found in saliva of healthy human adults (89MI1).

When patients with hyperalaninemia were loaded with tetrahydrobiopterin labeled at C3' with ^2H (90HCA1058), ^2H -labeled bipterin and ^2H -labeled primapterin were produced in equal amounts in their urine [90JBC(265)3923; 92HCA1237]. Furthermore, *in vitro* incubation of tetrahydropteridin-6-yl acyclo C-nucleosides, namely tetrahydrobiopterin (**633**) and tetrahydro-D-neopterin (**637**), with phenylalanine hydroxylase produced the two pteridin-7-yl acyclo C-nucleosides primapterin **625** and anapterin **646**, respectively [90BBR(172)1060]. These results led to the conclusion that pteridin-7-yl acyclo C-nucleosides are biologically formed from the corresponding pteridin-6-yl precursors by enzymatic intramolecular rearrangement processes [90BBR(172)1060, 90JBC(265)3923; 92HCA1237].

Before isolation from the natural sources, primapterin (**625**) was synthesized, together with bipterin (**615**) as explained in Scheme 163 (Section XI,C',1,a). Primapterin (**625**) was obtained as a single product by cyclocondensation of 2,5,6-triaminopyrimidin-4-one (**624**) with *aldehydo*-5-deoxy-L-arabinose semicarbazone (**647**) as a result of the regioselective addition of the most nucleophilic C5 amino function of **624** onto the azomethine of **647** (89MI2, 90HCA337) (Scheme 169). Anapterin (**646**) was also prepared according to this sequence of reactions from *aldehydo*-D-ribose semicarbazone and **623** (89MI2; 90HCA337).

3. *Pteridin-6-yl and Pteridin-7-yl Acyclo C-Nucleosides*

The first synthesis of these compounds by cyclocondensation of monosaccharides with 5,6-diaminopyrimidines was reported by Karrer and his group in 1947 (47HCA1031). Since then, a great deal of research work has been done on the synthesis of various members of pteridine acyclo C-nucleosides by this method or modifications therefrom. When ketose (**652**) or aldose (**653**) monosaccharides were cyclocondensed with 2,5,6-triamino-pyrimidin-4-one (**624**), 6- or 7-(alditol-1-yl)pteridin-4-ones (**656** or **658**) or mixtures of both were obtained [47HCA1031; 48HCA777, 48HCA782; 49HCA1041,

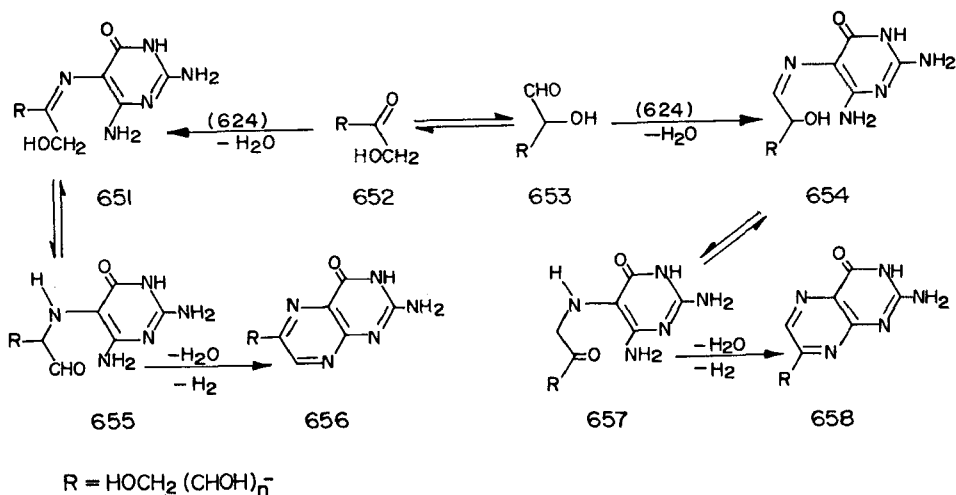


SCHEME 169

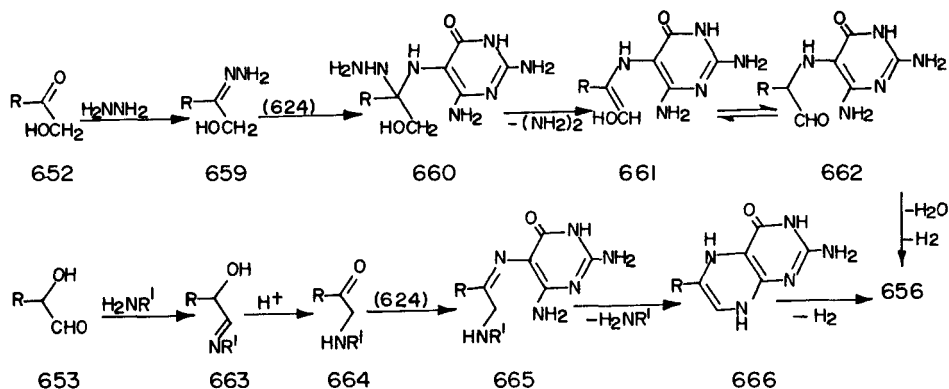
49JA3977, 49JCS79; 50LA(570)127; 52GEP839498, 52USP2603643; 54-USP2667485; 58JA2018; 63CB1406; 64CB1002; 68HCA1029; 71NKZ-1177; 81AQ(C)126; 82AQ(C)399]. According to the mechanism proposed for this reaction (Scheme 170), the most nucleophilic amino group at C5 of **624** attacks C1 of aldoses or C2 of ketoses.

Aldosuloses (sugar osones) also reacted with **624** to afford mixtures of 6- and 7-(alditol-1-yl)pteridin-4-ones (**656** and **658**) (47JA2566; 51USP-2541717).

In the presence of hydrazine hydrate, ketose (**652**) (49HCA1041, 49JA3977) and aldose (**653**) monosaccharides reacted with **624** to give the



SCHEME 170

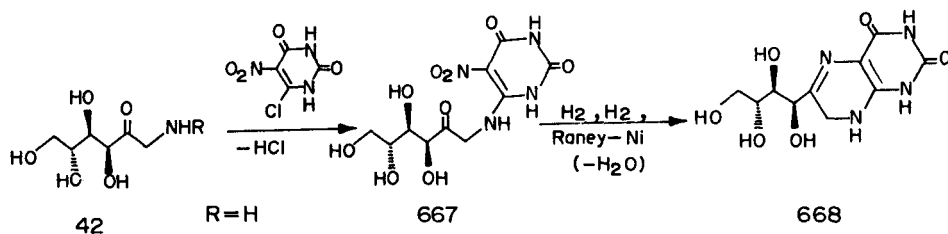


SCHEME 171

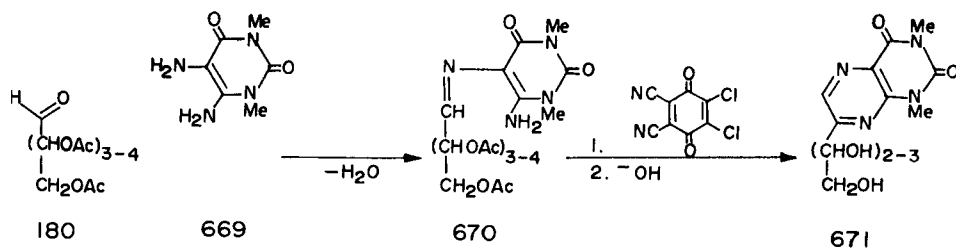
corresponding pteridin-6-yl acyclo C-nucleosides (**656**) only [48NAT(L)-308; 49CB25, 49HCA1041, 49JA3977, 49JCS79, 49JCS2077; 52JPJ1294; 58JA2018]. Aldose phenylhydrazones (**663**, $R' = \text{NHAr}$) (70HCA1202; 79BCJ181; 84LA1815), aldulose 1-arylhydrazones (56CB956), 1-alkyl-amino-1-deoxyketoses (**664**, $R' = \text{alkyl}$) (48E427; 68HCA1495), glycosylamines (49JCS2077), and monosaccharide phenylosazones (50SWP268531) behaved similarly. These results were explained in terms of an Amadori rearrangement of aldose hydrazones (**663**, $R' = \text{H, NHAr}$) to the corresponding 1-hydrazino-1-deoxyketoses (**664**, $R' = \text{H, NHAr}$), which then cyclocondense with **624** to give **656** as explained in Scheme 171.

7,8-Dihydro-6-(*D*-arabino-tetritol-1-yl)pteridine-2,4-dione **668** was unequivocally prepared by condensation of 1-amino-1-deoxy-*D*-fructose (**42**) with 6-chloro-5-nitrouracil followed by concomitant reduction and cyclization of **667** (62JCS44) (Scheme 172).

The 7-(alditol-1-yl)-1,3-dimethylpteridine-2,4-diones **671** were the only products obtained from the reaction of *aldehydo*-sugar acetates (**180**) with 5,6-diamino-1,3-dimethyluracil (**669**) followed by oxidative cyclization of



SCHEME 172



SCHEME 173

the formed Schiff bases **670** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [75JAP(K)75/129593] (Scheme 173).

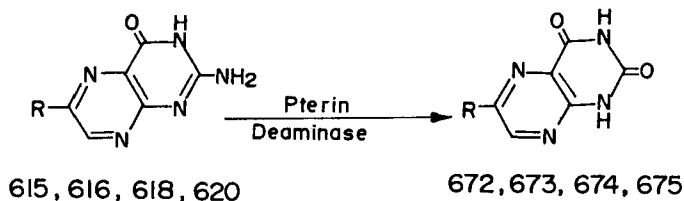
Enzymatic deamination of the naturally occurring pteridin-6-yl acyclo C-nucleosides biopterin (**615**), dictypterin (**616**), D-neopterin (**618**), and D-monapterin (**620**) with pterin deaminase from the slime mold *Dictyostelium discoideum* caused their conversion to the corresponding lumazin-6-yl {2,4-dioxypyrazino[2,3-*d*]pyrimidin-6-yl} acyclo C-nucleosides: biolumazine (**672**), dictyolumazine (**673**), D-neolumazine (**674**), and D-monolumazine (**675**), respectively (94MI2) (Scheme 174).

Some pteridine acyclo C-nucleosides revealed activities against tumors [52JPP1294; 75JAP(K)75/129593], bacteria [75JAP(K)75/129593], and viruses [54USP2667485; 75JAP(K)75/129593]. 3-*N*-Propylbiopterin (oncopterin) is a useful diagnostic marker for cancer [94GEP(D)4244261].

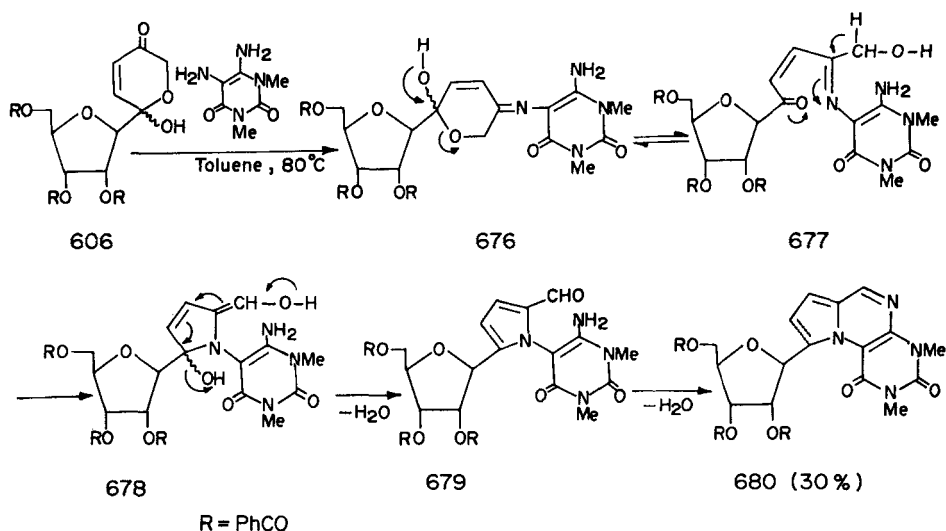
D'. PYRROLO[1',2':1,2]PYRAZINO[5,6-*d*]PYRIMIDINE C-NUCLEOSIDES

1. Pyrrolo[1',2':1,2]pyrazino[5,6-*d*]pyrimidin-1-yl C-Nucleosides

In addition to the pyrazino[2,3-*d*]pyrimidin-7-yl C-nucleoside **609** and its homo analog **614**, which were obtained by the reaction of 5,6-diamino-1,3-dimethyluracil with the 6-hydroxy-6- β -D-ribofuranosyl-2*H*-pyran-3(6*H*)-one derivative **606** (Section XI,B'; Scheme 162), the pyrrolo-pyrazino-pyrimidine C-nucleoside **680** was produced in 30% yield according to the mechanism outlined in Scheme 175 (89JOC3927).



SCHEME 174



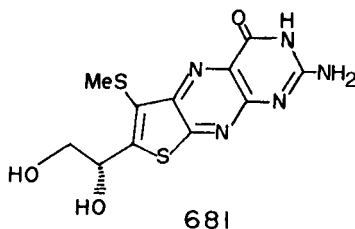
SCHEME 175

E'. THIENO[2',3':2,3]PYRAZINO[6,5-*d*]PYRIMIDINE ACYCLO C-NUCLEOSIDES

1. *The Naturally Occurring Thieno[2',3':2,3]pyrazino[6,5-*d*]pyrimidin-7-yl Acyclo C-Nucleosides "Urothione"*

Urothione was isolated from human urine [40ZPC(263)78; 43-ZPC(277)284], and its 2-amino-7-[(2'*S*)-1',2'-dihydroxyethyl]-6-(methylthio)thieno[2',3':2,3]pyrazino[6,5-*d*]pyrimidine} structure (**681**) was established on the basis of degradative and spectral studies (55CB1251; 67NKZ897, 67TL4507; 69MI3; 70MI6). The *S* configuration of C2' of the side chain has recently been established (95TL2631).

A mixture of the two enantiomers **688** of **681** was synthesized by Sakurai and Goto by elaborating the thiophene ring onto the 6-(4,5-dibenzyloxy-



2-oxopent-1-yl)pterin **685** (68TL2941; 69MI4) (Scheme 176). Taylor and Reiter synthesized the same enantiomeric mixture (**688**) by a different approach, which comprised forming the thieno[2,3-*b*]pyrazine acyclo *C*-nucleoside **694** and then constructing the pyrimidine ring (89JA285) (Scheme 177).

XII. Condensed 1,4-Diazine *C*-Nucleosides

A. PYRROLO[1,2-*a*]PYRAZINE *C*-NUCLEOSIDES

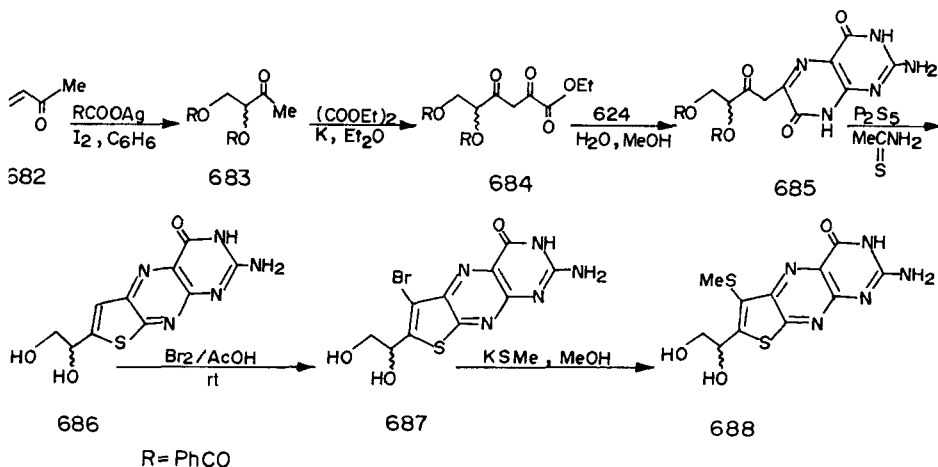
1. *Pyrrolo*[1,2-*a*]pyrazin-6-yl *C*-Nucleosides

Treatment of the β -ribofuranosylpyranone derivative **606** with 1,2-diaminoethane, and removal of the sugar-blocking groups, gave the 3,4-dihydro-6-(β -D-ribofuranosyl)pyrrolo[1,2-*a*]pyrazine **699** (88JOC1401) (Scheme 178).

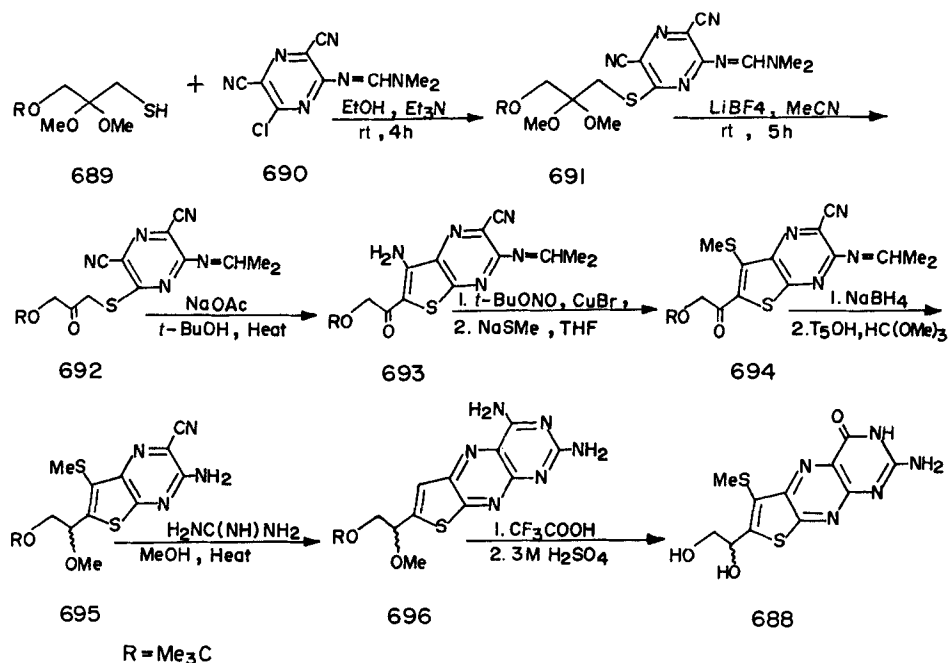
B. PYRROLO[1,2-*a*]PYRAZINE ACYCLO *C*-NUCLEOSIDES

1. *Bis*{*pyrrolo*[1,2:1',2'-*d*]}pyrazine-1,6-diyl Acyclo *C*-Nucleosides

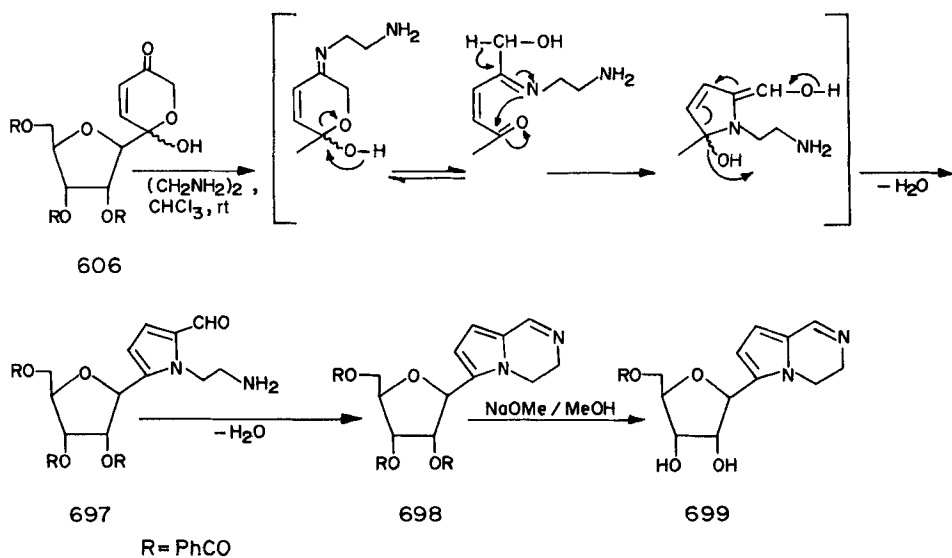
Treatment of 2-carboxy-3-methoxycarbonyl-5-(D-*arabino*-tetritol-1-yl)-pyrrole (**700**) with acetic anhydride caused bimolecular cyclocondensation with simultaneous *O*-acetylation to yield **701** (74MI8) (Scheme 179).



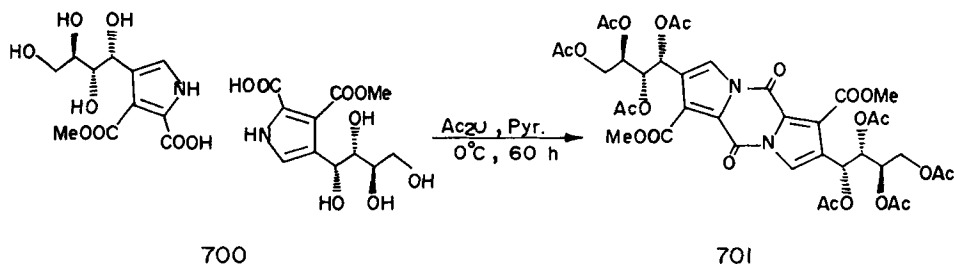
SCHEME 176



SCHEME 177



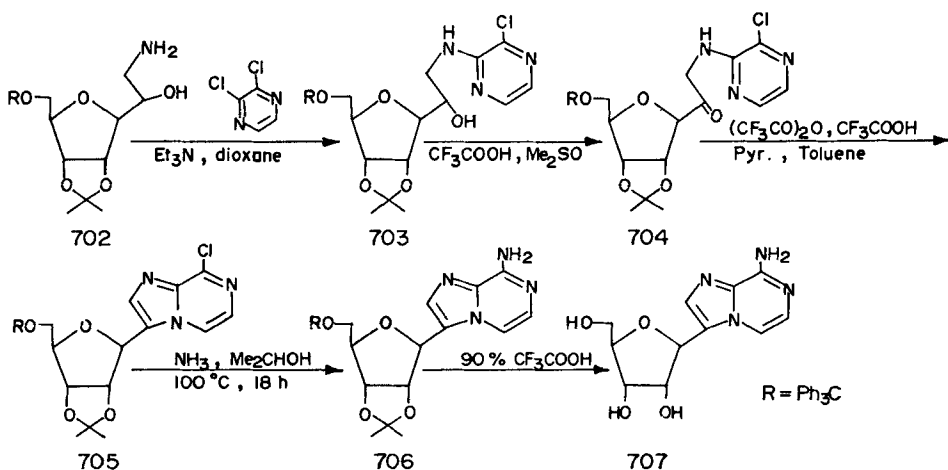
SCHEME 178



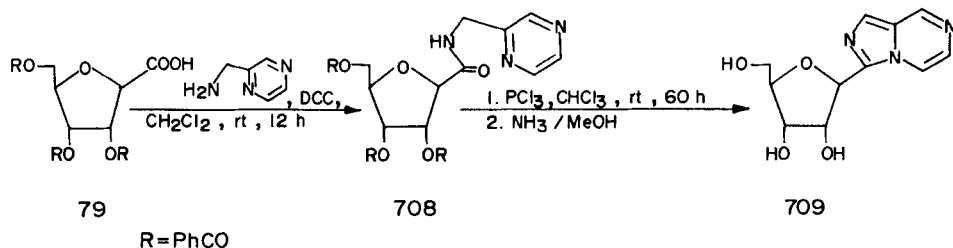
SCHEME 179

C. IMIDAZO[1,2-*a*]PYRAZINE C-NUCLEOSIDES1. *Imidazo*[1,2-*a*]pyrazin-3-yl C-Nucleosides

The 2-amino-1-(β -D-ribofuranosyl)ethanol derivative **702** was condensed with 2,3-dichloropyrazine to give **703**, which was elaborated to **707** [93JHC(31)1213] (Scheme 180). C-Nucleoside **707** demonstrated weak suppression of mouse splenic NK-cell activity toward YAC lymphoma cells and *in vivo* anti-inflammatory activity in rats [93JHC(31)1213].



SCHEME 180



SCHEME 181

D. IMIDAZO[1,5-*a*]PYRAZINE C-NUCLEOSIDES

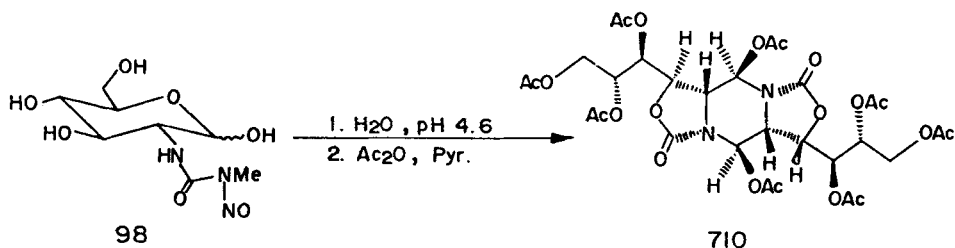
1. Imidazo[1,5-*a*]pyrazin-3-yl C-Nucleosides

The imidazole ring of the imidazo[1,5-*a*]pyrazin-3-yl C-nucleoside **709** was formed upon reacting the 2,5-anhydro-D-allonic derivative **79** with 2-aminomethylpyrazine, dehydrocyclization of the resulting amide **708**, and de-*O*-benzoylation of the protected C-nucleoside [84JCS(P1)229] (Scheme 181).

E. OXAZOLO[3,4-*a*]PYRAZINE ACYCLO C-NUCLEOSIDES

1. Bis{oxazolo[3,4-*a*:3',4'-*d*]}pyrazine-5,10-diyl Acyclo C-Nucleosides

In a saline solution at pH 4.6, the antibiotic streptozotocin **98** decomposed to a mixture of several products. Acetylation of this mixture and separation of the products gave the acetylated 5,10-di-(*D*-erythro-tritol-1-yl)-bisoxazolo[3,4-*a*:3',4'-*d*]pyrazine-3,8-dione **710** (79JOC9) (Scheme 182).

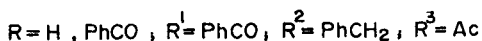
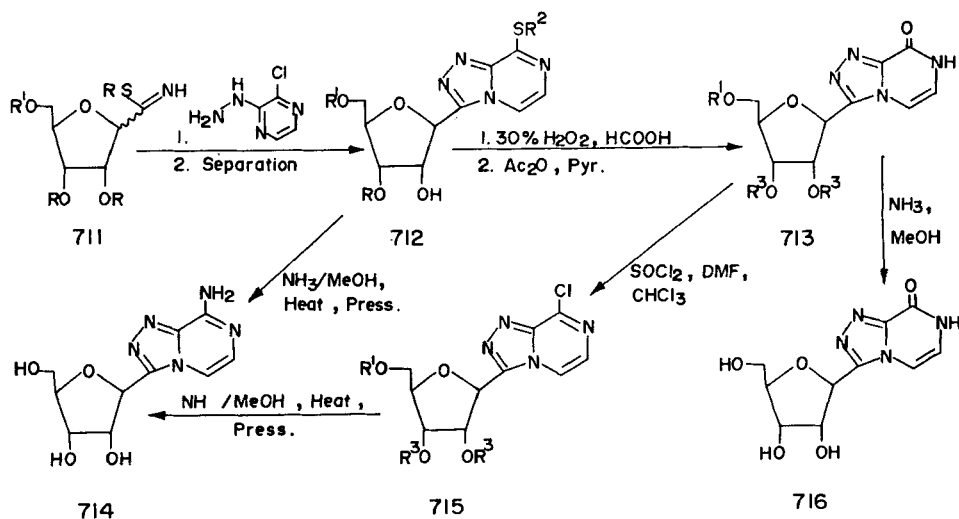


SCHEME 182

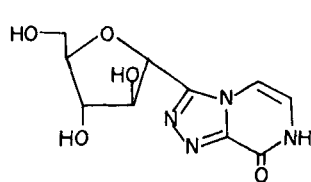
F. 1,2,4-Triazolo[4,3-*a*]pyrazine C-NUCLEOSIDES1. 1,2,4-Triazolo[4,3-*a*]pyrazin-3-yl C-Nucleosides

Benzyl D-ribofuranosylthioformimidates (**711**) reacted with 3-chloro-2-hydrazinopyrazine to form the 8-benzylthio-1,2,4-triazolo[4,3-*a*]pyrazin-3-yl C-nucleosides **712** as a result of nucleophilic displacement of the chloro group by the benzyl mercaptan produced from the initial cyclocondensation step. Compounds **713** were transformed to the formycin and formycin analogs **714** and **716** (79JOC1028; 84JMC924) (Scheme 183). Compound **714** inhibited growth of L1210 tumor cells in culture, has weak antiviral activity, and acted as a coronary vasodilator (84JMC924).

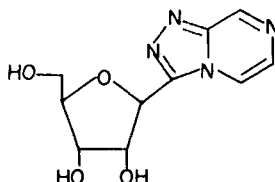
The 3-(α -D-arabinofuranosyl)-1,2,4-triazolo[4,3-*a*]pyrazin-8-one **717** (79-



SCHEME 183



717



718

MI1) and the unsubstituted 3-(β -D-ribofuranosyl)-1,2,4-triazolo[4,3-*a*]pyrazine **718** (89MI5) were synthesized by similar reactions.

G. QUINOXALINE C-NUCLEOSIDES

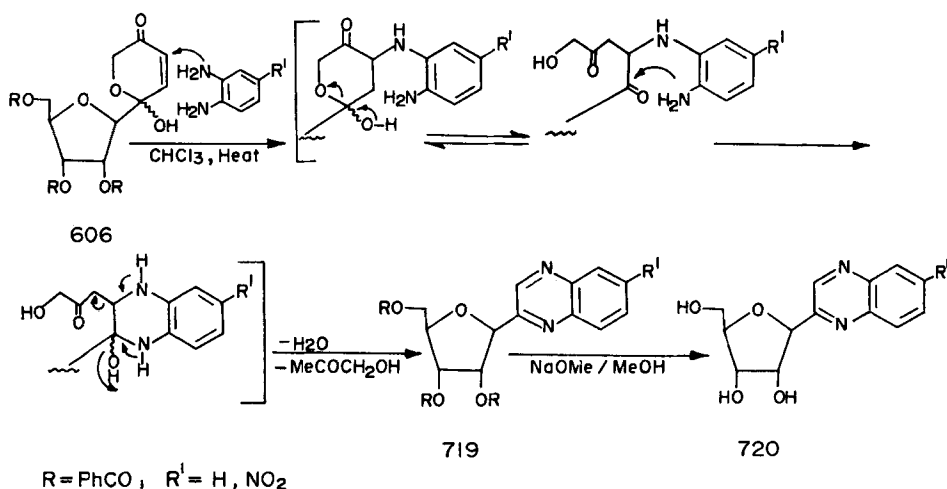
1. Quinoxalin-2-yl C-Nucleosides

Heating the 6-hydroxy-6- β -D-ribofuranosylpyranone derivative (**606**) with 1,2-diaminobenzenes gave the quinoxalin-2-yl C-nucleosides **720** (Scheme 184) in addition to the pyrrolo[1,2-*a*]quinoxalin-1-yl C-nucleosides **744** (Section XII,J; Scheme 191) [88JOC1401; 90JCS(P1)67].

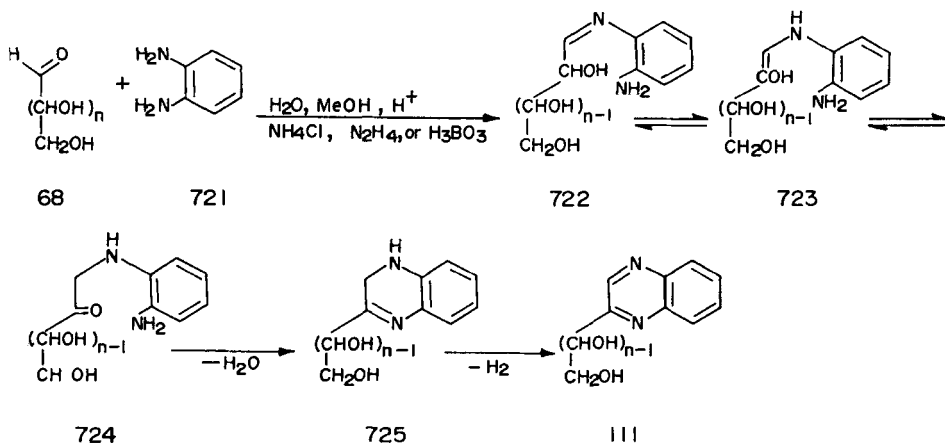
H. QUINOXALINE ACYCLO C-NUCLEOSIDES

1. Quinoxalin-2-yl Acyclo C-Nucleosides

Reaction of 1,2-diaminobenzene (**721**) with aldoses (**68**) may only involve the C1 of the sugar to afford the corresponding 2-(alditol-1-yl)benzimidazoles (**112**) (Section IV,C; Scheme 34) or C1 and C2 to give the 2-(alditol-1-yl)quinoxaline **111** (1887CB281, 188CB2205; 34CB1980, 44CB507; 53MI1; 58UK179; 63JOC231; 66ZC329; 68JA1318; 79HCA241; 84ABC2753). 2-Amino-2-deoxyaldoses also reacted with 1,2-diaminobenzene (**721**) to give



SCHEME 184



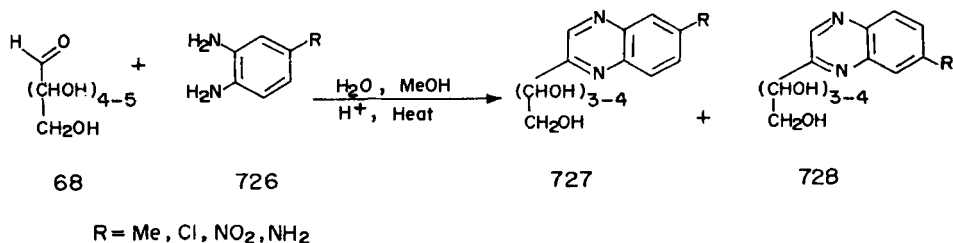
SCHEME 185

111 [43JBC(150)351]. The mechanism according to which compounds **111** are formed is shown in Scheme 185 (47CB255).

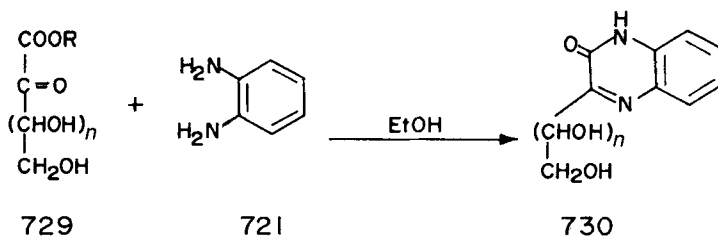
Ketoses (34CB155; 41CB13; 68JA1318), 1-amino-1-deoxyketoses (Ama-dori compounds) [44CB507; 47CB255; 48E427; 58RTC827; 59ZN(B)217; 65LA(684)146; 88MI9], aldoses [1889CB87; 37BJ(31)1033; 41CB18; 59CB501], aldoses 1-arylhydrazones [54CB1068; 56CB956; 58CB1605; 58CB2273; 59CB501; 65LA(684)146], and reducing disaccharides (58-CB2273; 85ABC3279) also reacted with **721** to afford the corresponding quinoxalin-2-yl acyclo C-nucleosides.

Whenever 4-substituted-1,2-diaminobenzenes (**726**) were used, mixtures of 6- and 7-substituted quinoxalin-2-yl C-nucleosides (**727** and **728**) were obtained in which the 6-substituted isomer **727** usually predominated [56CB956; 58CB1605; 63JOC231; 65LA(684)146] (Scheme 186).

Condensation of 2-ketoaldonic acids (ulosonic acids, **729**) or their esters with **721** gave the 2-(alditol-1-yl)quinoxalin-3-ones **730** (34CB155; 37CB2148; 61CB1743; 69HCA300) (Scheme 187).



SCHEME 186



SCHEME 187

2,3-Diketohexono-1,4-lactones (2,3-hexodiulosono-1,4-lactones, **190**) reacted with 1,2-diaminobenzenes in the presence of hydrazines to give the 2-(1-hydrazonotetritol-1-yl)quinoxalin-3-ones **732** through intermediate **731** (34CB555; 57AG479; 59CB1550; 65HCA1860; 78MI5, 78MI7, 78MI9, 78MI10; 80MI6; 86MI3; 88MI10) (Scheme 188).

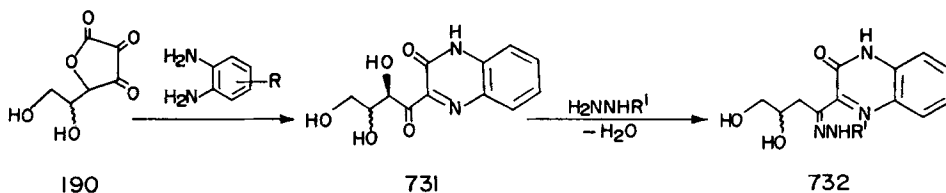
2-[(3*S*)-3,4-dihydroxybutyl]-3-methylquinoxaline **740** was prepared as shown in Scheme 189 by reacting the 5-hydroxy-5-(β-D-ribofuranosyl)furanone derivative **247** with 1,2-diaminobenzene [93H(36)2591].

Conformations of quinoxalin-2-yl acyclo *C*-nucleosides (65JOC2457) and the relation between the stereochemistry at C1' and the sign of the Cotton effect of their ORD spectra were studied (67JA4129; 68JA1318). Polarographic reduction of some derivatives of these acyclo *C*-nucleosides was also investigated (86MI5).

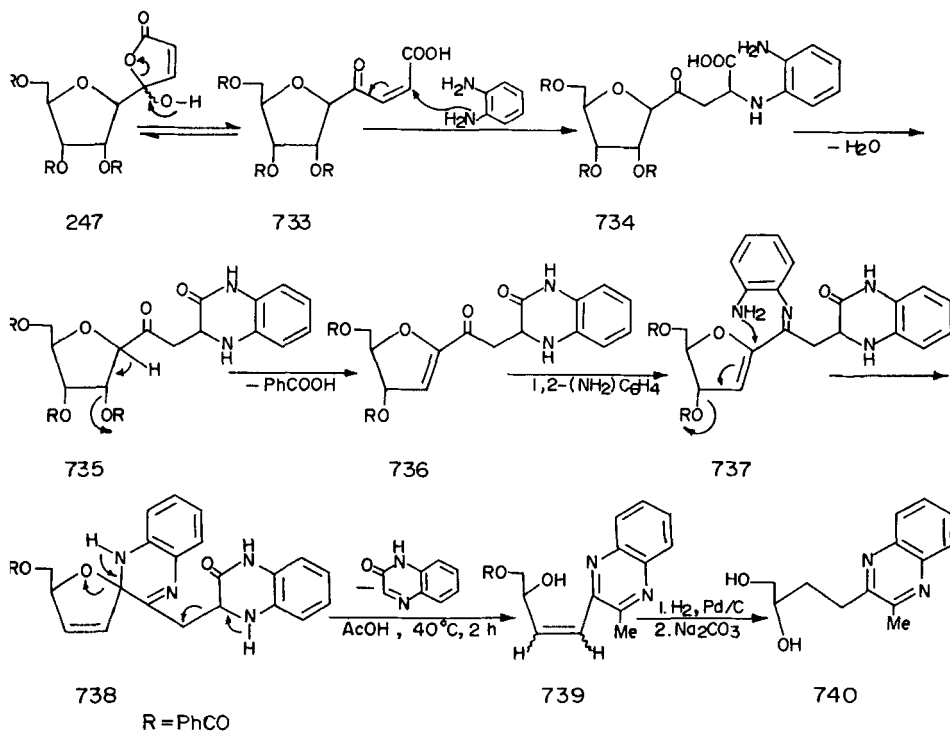
I. PYRIDO[2,3-*b*]PYRAZINE ACYCLO *C*-NUCLEOSIDES

1. *Pyrido*[2,3-*b*]pyrazin-3-yl *C*-Nucleosides

In the presence of phenylhydrazine, dehydro-L-ascorbic acid (**741**) reacted with 2,3-diamino-5-bromopyridine to produce a product that was assigned the 7-bromo-3-(1-phenylhydrazono-2,3,4-trihydroxybutyl)pyrido[2,3-*b*]pyrazin-2-one structure **742**. No rationale was offered as to why the possible alternative 6-bromo isomer (**743**) was excluded (64AGE802) (Scheme 190).



SCHEME 188

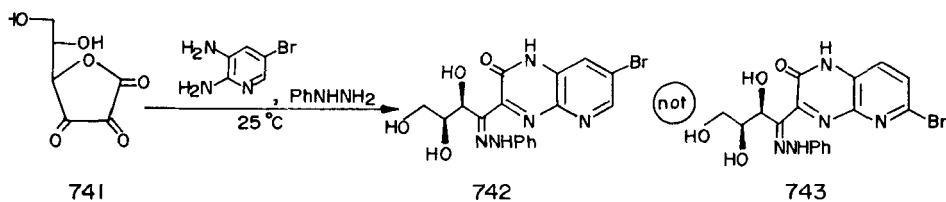


SCHEME 189

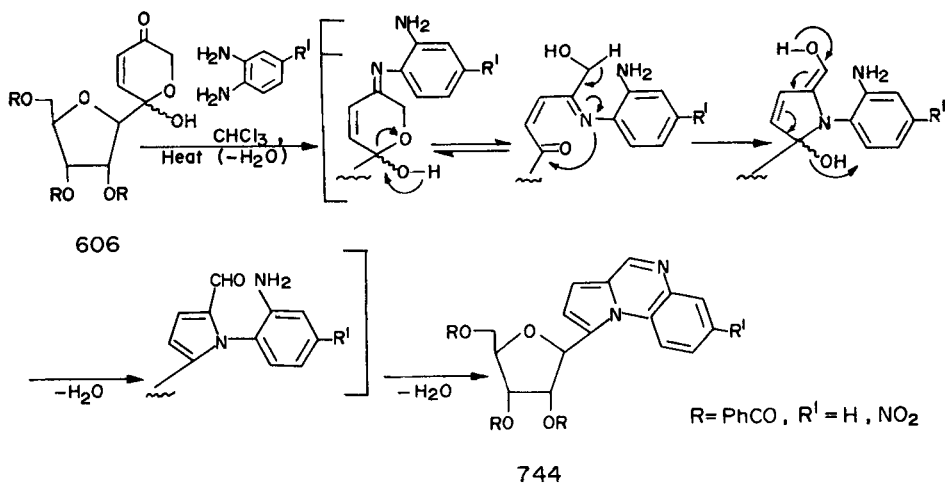
J. PYRROLO[1,2-*a*]QUINOXALINE C-NUCLEOSIDES

1. Pyrrolo[1,2-*a*]quinoxalin-1-yl C-Nucleosides

In addition to the quinoxalin-2-yl C-nucleosides **720** (Section XII,G; Scheme 184) formed upon reacting **606** and 1,2-diaminobenzenes, the pyrrolo[1,2-*a*]quinoxalin-1-yl C-nucleoside **744** was formed in 16% yield according to the mechanism shown in Scheme 191 [88JOC1401; 90JCS(P1)67].



SCHEME 190



SCHEME 191

K. FURO[2,3-*b*]QUINOXALINE ACYCLO C-NUCLEOSIDES

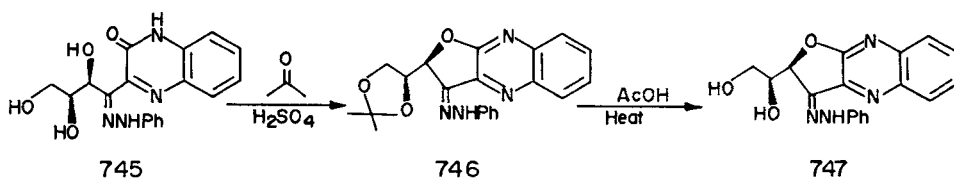
1. Furo[2,3-*b*]quinoxalin-3-yl Acyclo C-Nucleosides

During *O*-isopropylidenation of the alditolyl chain of the 3-(alditol-1-yl)quinoxalin-2-one **745**, the fused furan ring of **746** was formed as a result of acid-catalyzed cyclodehydration of the enolized C2 carbonyl and C2' OH groups. Removal of the ketal group of **746** gave **747** (93MI6) (Scheme 192).

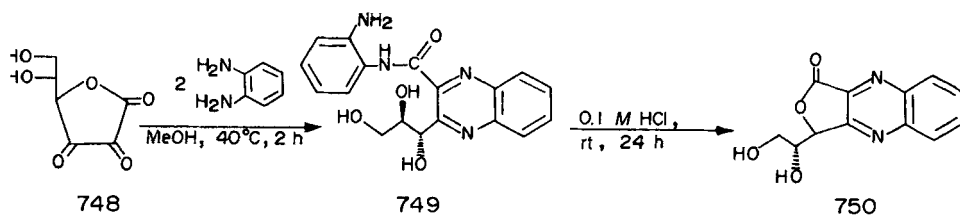
L. FURO[3,4-*b*]QUINOXALINE ACYCLO C-NUCLEOSIDES

1. Furo[3,4-*b*]quinoxalin-2-yl Acyclo C-Nucleosides

Reaction of dehydro-D-*arabino*-ascorbic acid (**748**) with two molar equivalents of 1,2-diaminobenzene gave the quinoxalin-2-yl derivative **749**. Treatment of the latter with hydrochloric acid hydrolyzed the 2-aminobenzamido



SCHEME 192



SCHEME 193

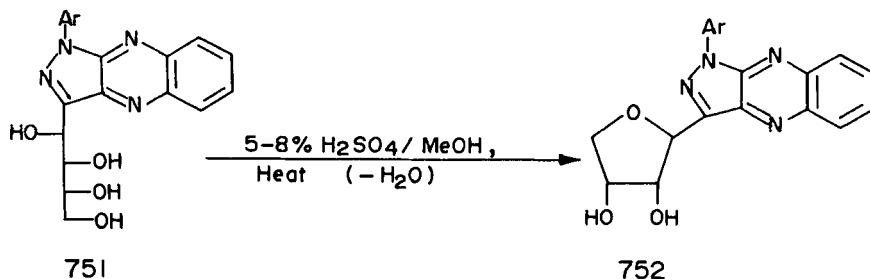
group with lactonization of the produced acid to yield the 2-(alditol-1-yl)furo[3,4-*b*]quinoxalin-9-one **750** (84MI9) (Scheme 193).

M. PYRAZOLO[3,4-*b*]QUINOXALINE (FLAVAZOLE) C-NUCLEOSIDES

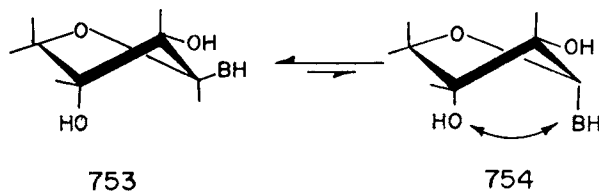
1. *Pyrazolo[3,4-*b*]quinoxalin-3-yl C Nucleosides* (*Flavazol-3-yl C-Nucleosides*)

The only synthetic pathway used so far to prepare these *C*-nucleosides was the acid-catalyzed cyclodehydration of the alditolyl chains of their acyclo analogs (Section XII.N). Thus, heating 1-aryl-3-(*D-arabino*-tetritol-1-yl)flavazoles (**751**) with dilute sulfuric acid gave, stereospecifically, 1-aryl-3-(β -*D*-erythrofuranosyl)flavazoles (**752**) (78MI7; 80MI8; 82MI4; 84MI5; 96MI1) (Scheme 194).

During this cyclodehydration, inversion of configuration occurred at C1' of **751** to give the β -*D*-*C*-nucleoside **752** rather than its α -anomer because of (i) preference of the protonated bulky heterocycle to occupy the equatorial β position in the 2E (envelope) conformation (**753**) to gain the stabilization of the reverse anomeric effect, and (ii) destabilization of the 2E conformation of the alternative α -anomer (**754**) by the nonbonded *cis*-1,3-diaxial interaction between the C3' hydroxyl and the bulky heterocycle (80MI8) (Scheme 195).



SCHEME 194



B = 1-Arylfavazol-3-yl

SCHEME 195

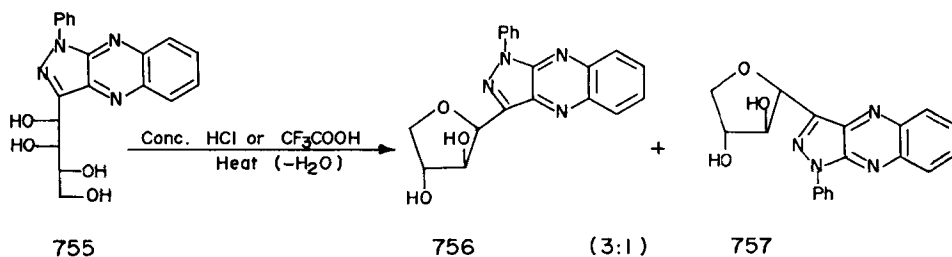
However, the outcome of the acid-catalyzed cyclodehydration of 1-phenyl-3-(*D*-*lyxo*-tetritol-1-yl) flavazole (**755**) was stereoselective, since it produced a mixture of 1-phenyl-3-(β - and α -*D*-threofuranosyl)flavazoles (**756** and **757**) in the ratio 3 : 1. The α -anomer **757** is stereochemically more stable because the bulky heterocycle and the C2' hydroxyl occupy less crowded positions than in the β -anomer **756** (94MI8) (Scheme 196).

Flavazole *C*-nucleosides revealed cytotoxic activity against the human nasopharynx KB epidermoid carcinoma cells (82MI4; 84MI5) and mouse P388 leukemia cells (84MI5).

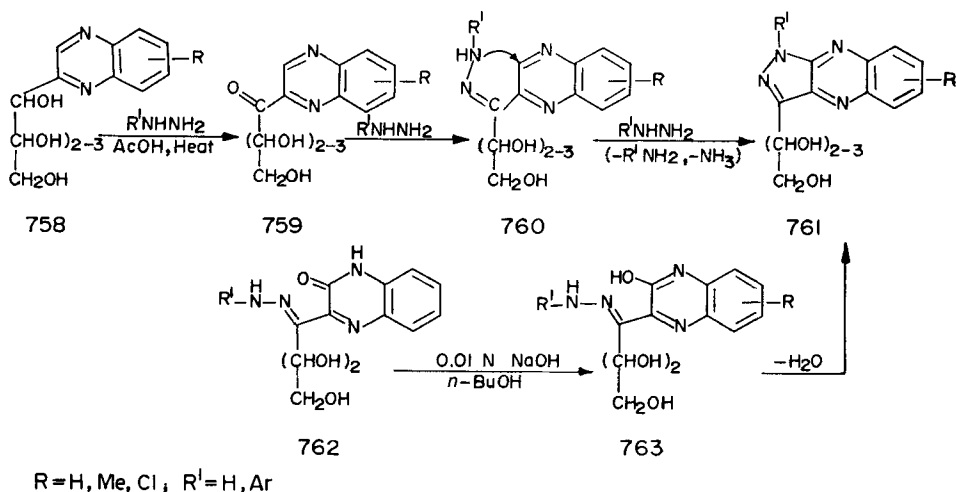
N. PYRAZOLO[3,4-*b*]QUINOXALINE (FLAVAZOLE) ACYCLO *C*-NUCLEOSIDES

1. *Pyrazolo*[3,4-*b*]quinoxalin-3-yl *C*-Nucleosides (*Flavazol*-3-yl *Acyclo C*-Nucleosides)

Quinoxalin-2-yl acyclo *C*-nucleosides (**758**) (Section XII,H) react with three molar equivalents of hydrazine (43CB1; 71MI4) or arylhydrazines (41CB13, 41CB279, 41CB398; 42CB1536; 44CB507; 53MI1;



SCHEME 196



SCHEME 197

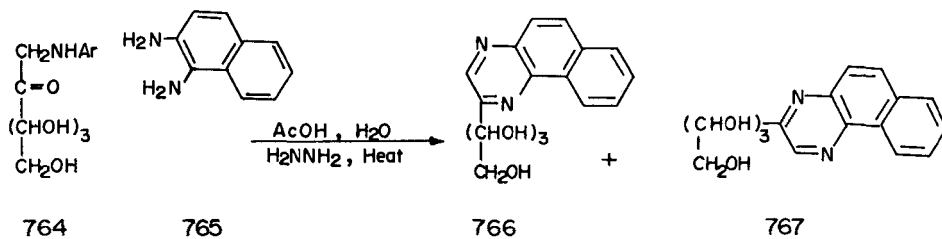
58CB1605, 58MI1; 59ZN(B)217; 63JOC999; 66ZC329; 71ZC380; 72JPR877] to give flavazol-3-yl acyclo C-nucleosides (**761**) (Scheme 197). 3-(1-Arylh-drazono-2,3,4-trihydroxybutyl)quinoxalin-2-ones (**762**) (Section XII,H; Scheme 188) undergo base-catalyzed cyclodehydration to give **761** also [57AG479; 59CB1550; 78MI5, 78MI8, 78MI9, 78MI10; 86MI3; 89MI7, 89MI8; 92MI3; 93H(36)961] (Scheme 197).

Flavazol-3-yl derivatives of oligosaccharides were prepared, mainly, as useful derivatives to characterize these oligosaccharides [46MI1, 46MI2; 52JBC(196)265; 53JA3664; 54JA1671; 55JA1015; 58CB2273, 58JA1445, 58MI1; 62MI1; 69CCC1118; 71JPR940, 71MI5, 71ZC380; 72JPR877, 72MI3]. UV (61SCI112), ORD (67JA4129), CD (78MI6; 86MI8), and MS (70OMS1535; 71MI6, 71MI7) spectral properties, as well as the relation between the configuration of the alditolyl chains and their preferred conformation, were studied (86MI7).

O. BENZO[*f*]QUINOXALINE ACYCLO C-NUCLEOSIDES

1. Benzo[*f*]quinoxalin-2- and 3-yl Acyclo C-Nucleosides

Reaction of 1-arylmino-1-deoxyketoses (**764**) with 1,2-diaminonaphthalene (**765**) in the presence of hydrazine hydrate gave a mixture of the 2- and 3-(alditol-1-yl)benzo[*f*]quinoxalines **766** and **767**, respectively, in the ratio of 2.5:1 (58CB101) (Scheme 198).



SCHEME 198

P. BENZO[g]QUINOXALINE ACYCLO C-NUCLEOSIDES

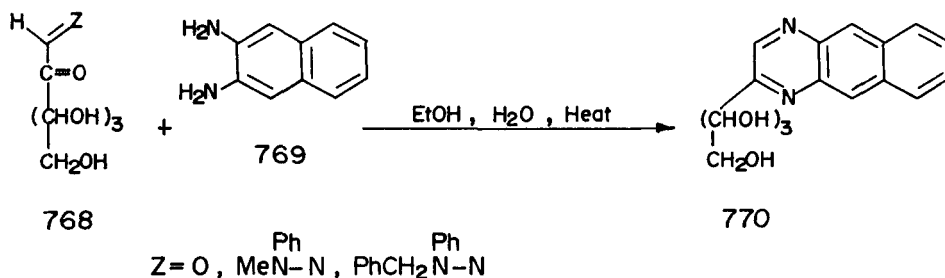
1. Benzo[g]quinoxalin-2-yl Acyclo C-Nucleosides

Acyclo C-nucleosides of this class (**770**) were prepared by cyclocondensation of alduloses (**768**, Z = O) or their hydrazones [**768**; Z = Me(Ph)NN, PhCH₂(Ph)NN] with 2,3-diaminonaphthalene (**769**) (58CB101) (Scheme 199).

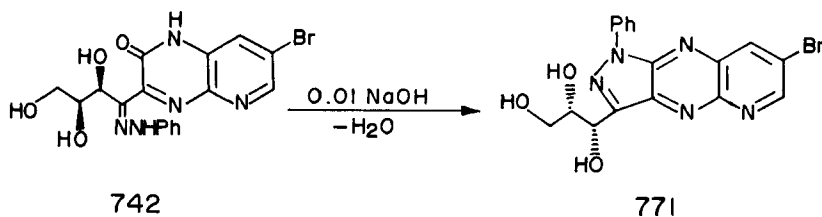
Q. PYRIDO[2,3-*c*]PYRAZOLO[3,4-*b*]PYRAZINE ACYCLO C-NUCLEOSIDES

1. Pyrido[2,3-*c*]pyrazolo[3,4-*b*]pyrazin-3-yl Acyclo C-Nucleosides

The 1-phenylpyrazole ring of the acyclo C-nucleoside **771** was formed as shown in Scheme 200 by the base-catalyzed cyclodehydration of the imidic acid hydroxyl and hydrazono proton of the pyrido[2,3-*b*]pyrazin-3-yl acyclo C-nucleoside **742** (Section XII,I; Scheme 190) (64AGE802).



SCHEME 199



SCHEME 200

R. BENZO[g]PYRAZOLO[3,4-b]QUINOXALINE ACYCLO C-NUCLEOSIDES

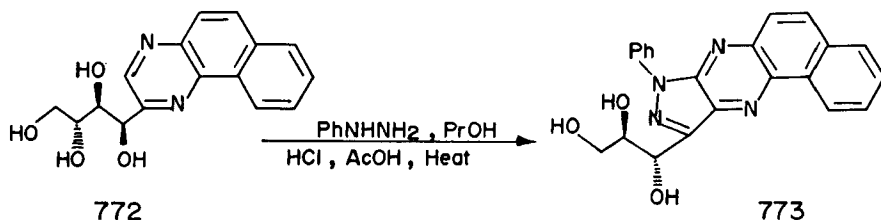
1. *Benzo[g]pyrazolo[3,4-b]quinoxalin-3-yl C-Nucleosides* *{benzo[g]flavazol-3-yl Acyclo C-Nucleosides}*

Reaction of 2-(D-arabino-tetritol-1-yl)benzo[f]quinoxaline (**772**) (Section XII,O) with three molar equivalents of phenylhydrazine gave the 3-(D-erythro-1,2,3-hydroxypropyl)benzo[g]flavazole **773** (58CB113) (Scheme 201).

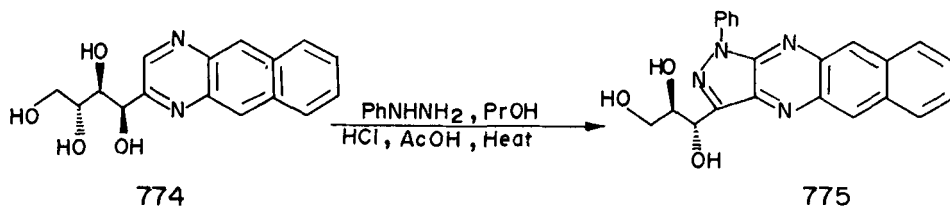
S. BENZO[h]PYRAZOLO[3,4-b]QUINOXALINE ACYCLO C-NUCLEOSIDES

1. *Benzo[h]pyrazolo[3,4-b]quinoxalin-3-yl C-Nucleosides* *{Benzo[h]flavazol-3-yl Acyclo C-Nucleosides}*

Applying the just-mentioned reaction to the benzo[g]quinoxalin-2-yl acyclo C-nucleoside **774** (Section II,P) gave **775** (58CB113) (Scheme 202).



SCHEME 201



SCHEME 202

T. BENZO[*i*]PYRAZOLO[3,4-*b*]QUINOXALINE ACYCLO C-NUCLEOSIDES

1. *Benzo[*i*]pyrazolo[3,4-*b*]quinoxalin-3-yl C-Nucleosides* *{Benzo[*i*]flavazol-3-yl Acyclo C-Nucleosides}*

Compound **777** of this type of acyclo C-nucleoside was prepared from the benzo[*g*]quinoxalin-3-yl precursor **776** (Section XII,O) by reaction with phenylhydrazine (58CB113) (Scheme 203).

U. QUINOXALINO[7',6':2,3]QUINOXALINE ACYCLO C-NUCLEOSIDES

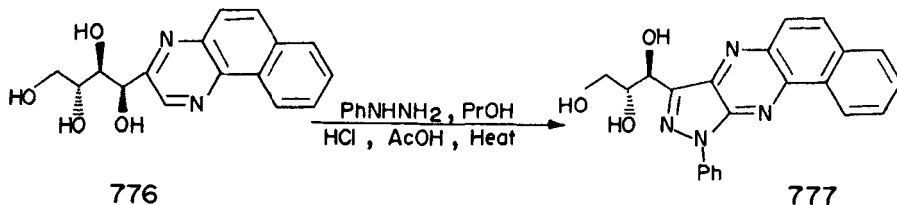
1. *Quinoxalino[7',6':2,3]quinoxalin-2-yl Acyclo C-Nucleosides*

Reaction of 1-(*N*-methyl-*N*-phenylhydrazono)-D-*arabino*-hexulose (**778**) with 2,3-diaminophenazine (**779**) produced **780** (58CB101) (Scheme 204).

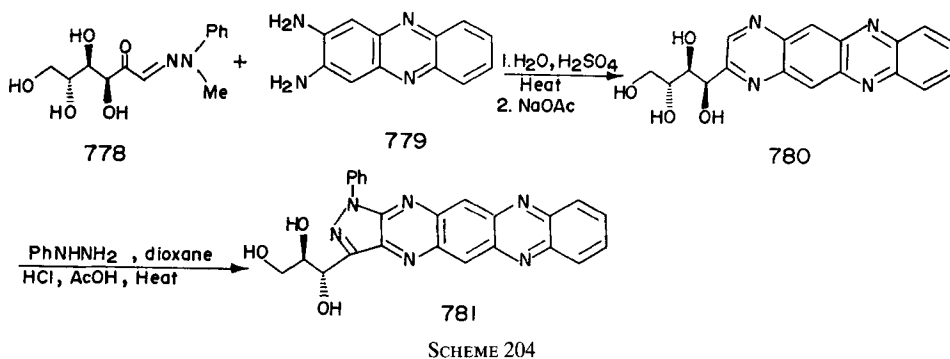
V. PYRAZOLO[3,4-*b*]QUINOXALINO[7',6':2,3]QUINOXALINE ACYCLO C-NUCLEOSIDES

1. *Pyrazolo[3,4-*b*]quinoxalino[7',6':2,3]quinoxalin-3-yl* *Acyclo C-Nucleosides*

The known example **781** of these compounds was obtained by reacting **780** with phenylhydrazine (58CB113) (Scheme 204).



SCHEME 203



SCHEME 204

XIII. Condensed Oxazine C-Nucleosides

A. PYRROLO[3,2-*d*]OXAZINE C-NUCLEOSIDES

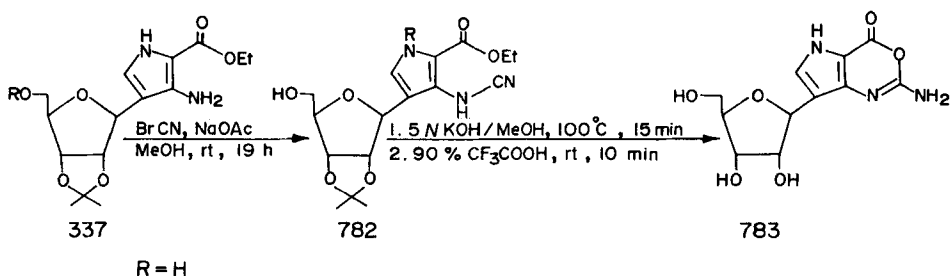
1. Pyrrolo[3,2-*d*]oxazin-3-yl C-Nucleosides

Construction of the oxazine ring of **783** was achieved by cyanation of the 4-amino-4-ethoxycarbonyl-pyrrol-3-yl C-nucleoside **337** with cyanogen bromide, followed by hydrolysis and cyclization of the ester cyanamide **782** with methanolic potassium hydroxide. Removal of the sugar-protective ketal group gave **783**, which possessed immunostimulant properties [85TL5785; 86JAP(K)86/260094] (Scheme 205).

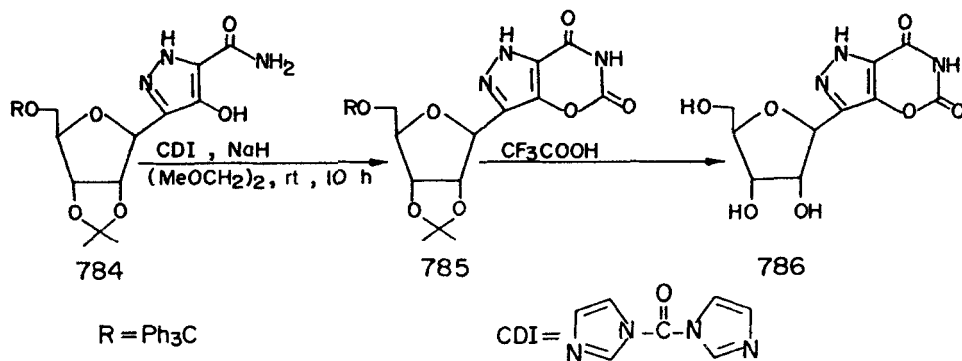
B. PYRAZOLO[4,3-*d*]OXAZINE C-NUCLEOSIDES

1. Pyrazolo[4,3-*d*]oxazin-3-yl C-Nucleosides

The synthesis of the 3- β -ribofuranosylpyrazolo[4,3-*d*]oxazine-5,7-dione **409** as an intermediate during the synthesis of formamycin B (**387**) is included in Scheme 115 [71JCS(CC)986].



SCHEME 205



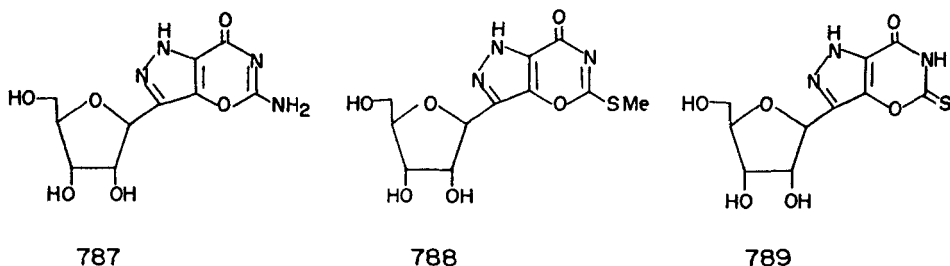
SCHEME 206

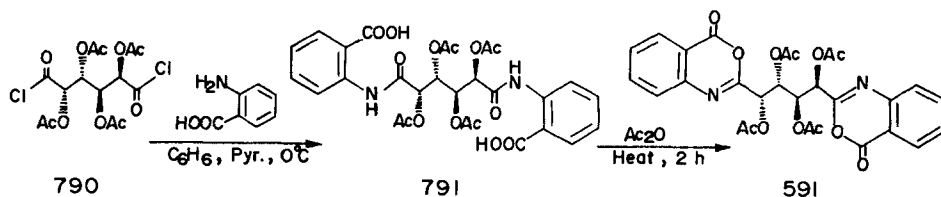
C. PYRAZOLO[3,4-*e*]OXAZINE C-NUCLEOSIDES

1. *Pyrazolo[3,4-*e*]oxazin-3-yl C-Nucleosides*

3-β-Ribofuranosylpyrazolo[3,4-*e*]oxazin-5,7-dione (**786**), the isomer of xanthosine and oxoformycin B (**388**), was prepared by carbonylation of the *O*-protected pyrazofurin **784** [97AHC(68)223] with 1,1'-carbonyldiimidazole (CDI) [84JAP(K)84/184176, 84JCS(P1)553; 87MIP1, 87USP 4656260] (Scheme 206). *C*-Nucleoside **786** has cytotoxic and virucidal activities equivalent or superior to those of pyrazofurin (87MIP1, 87USP4656260); **786** appears to act as a prodrug of pyrazofurin (91JMC1951).

Similar synthetic sequences to that shown in Scheme 206 were used for the preparation of the three pyrazol[3,4-*e*]oxazine *C*-nucleosides **787–789** (85MI3; 91JMC1951). The guanosine isomer **787** showed marginal cytotoxicity toward L1210 leukemia cells (91JMC1951).





SCHEME 207

D. BENZO[*d*]OXAZINE ACYCLO C-NUCLEOSIDES

1. Benzo[*d*]oxazin-2-yl Acyclo *C*-Nucleosides

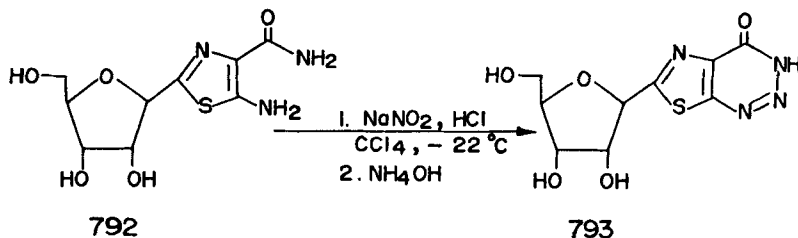
Condensation of tetra-*O*-acetylgalactaroyl dichloride (**790**) with anthranilic acid formed the bis-amide **791**, which was cyclodehydrated to the bis[4-oxobenzo[*d*]oxazin-2-yl] acyclo *C*-nucleoside **591** (87MI4) (Scheme 207). Compound **591** was used in the synthesis of the double-headed quinazolin-8-yl acyclo *C*-nucleosides **592** (Section XI,X; Scheme 158).

XIV. Condensed 1,2,3-Triazine C-Nucleoside

A. THIAZOLO[5,4-*d*]1,2,3-TRIAZINE C-NUCLEOSIDES

1. Thiazolo[5,4-*d*]1,2,3-triazin-2-yl *C*-Nucleosides

Treatment of the 5-amino-4-carboxamido-2-β-D-ribofuranosylthiazole **792** with sodium nitrite and hydrochloric acid effected the formation of the 1,2,3-triazinone ring of **793** (85JOC1741) (Scheme 208). This *C*-nucleoside was not superior to tiazofurin (4-carboxamido-2-β-D-ribofuranosylthiazole) [97AHC(68)223] against P388 and L1210 leukemic cells or Lewis lung carcinoma in culture (85JOC1741).



SCHEME 208

XV. Condensed 1,2,4-triazine C-Nucleosides

A. PYRROLO[2,1-*f*]1,2,4-TRIAZINE C-NUCLEOSIDES

1. *Pyrrrolo*[2,1-*f*]1,2,4-triazin-7-yl C-Nucleosides

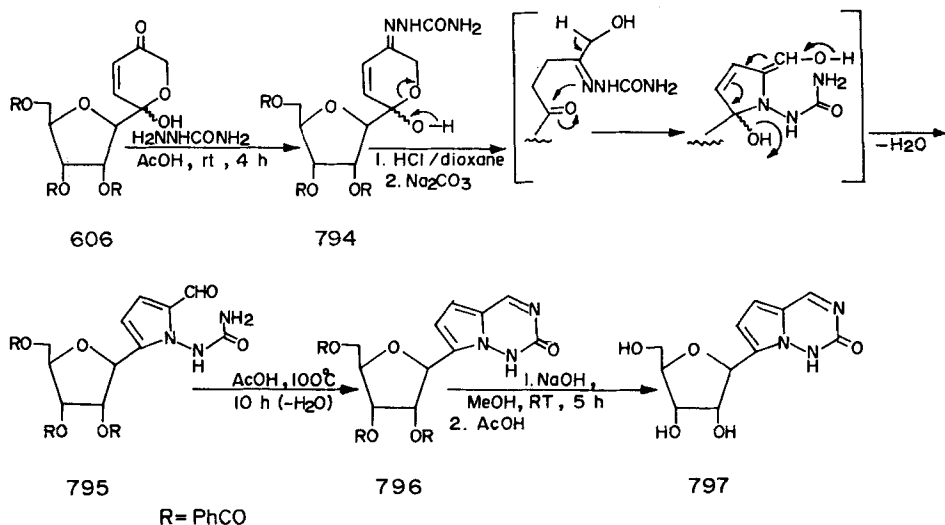
Under slightly acidic conditions, the pyran ring of the semicarbazone **794** underwent contraction to the 2-formyl-1-ureidopyrrol-5-yl C-nucleoside **795**. The latter was cyclodehydrated to **796** and de-*O*-protected to **797** [92H(34)569] (Scheme 209).

Klein and his group synthesized the 4-aminopyrrolo[2,1-*f*]1,2,4-triazin-7-yl C-nucleoside **803** that is related to formycin by multistep annulation of the 1,2,4-triazine ring onto the pyrrol-2-yl C-nucleoside **798** (94TL5339) (Scheme 210). C-Nucleoside **803** established pronounced *in vitro* growth-inhibitory activities against L-1210-C2, S180, and HL60-JG neoplastic cell lines (94TL5339).

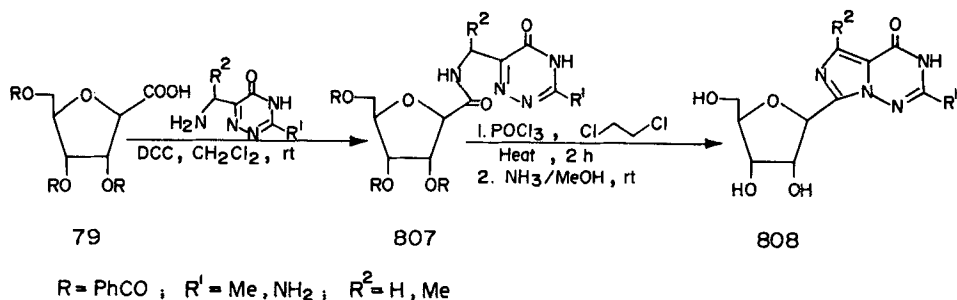
B. PYRROLO[1,5-*d*]1,2,4-TRIAZINE C-NUCLEOSIDES

1. *Pyrrrolo*[1,5-*d*]1,2,4-triazin-8-yl C-Nucleosides

The 3-formyl-4-β-D-ribofuranosylpyrrole **804** was elaborated to **806** by reaction with methyl hydrazinocarboxylate to give the corresponding hydra-



SCHEME 209



SCHEME 212

D. IMIDAZO[5,1-*f*]1,2,4-TRIAZINE ACYCLO C-NUCLEOSIDES

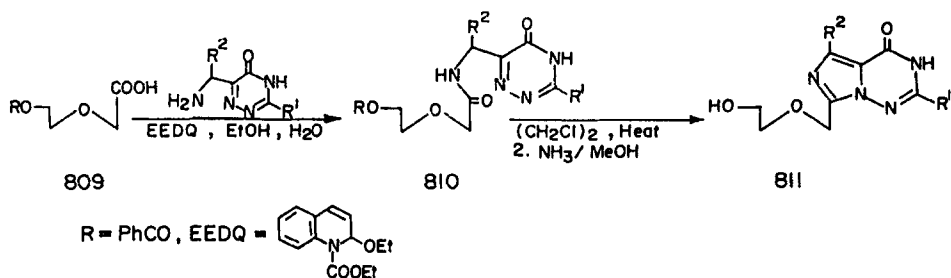
1. Imidazo[5,1-*f*]1,2,4-triazin-7-yl Acyclo C-Nucleosides

The acyclo C-nucleoside **811** was prepared in a closely similar plan to that used for the synthesis of its cyclic analog **808**. [2-(Benzoyloxy)ethoxy]-acetic acid was condensed with 6-aminomethyl-1,2,4-triazin-5-one to give amide **810**, which was then cyclized and de-*O*-benzoylated to **811**. This truncated sugar acyclo C-nucleoside did not inhibit herpes simplex viruses (HSV-1 and HSV-2) in cell culture (84JHC697) (Scheme 213).

E. 1,2,4-TRIAZOLO[3,4-*f*]1,2,4-TRIAZINE C-NUCLEOSIDES

1. 1,2,4-Triazolo[3,4-*f*]1,2,4-triazin-3-yl C-Nucleosides

The 1,2,4-triazolo[3,4-*f*]1,2,4-triazin-3-yl C-nucleoside **814**, related to guanosine, was obtained by cyclocondensation of 3,4,5-tri-*O*-benzoyl-2,5-anhydro-D-allonoyl chloride (**812**) with 3-amino-6-hydrazino-1,2,4-triazin-



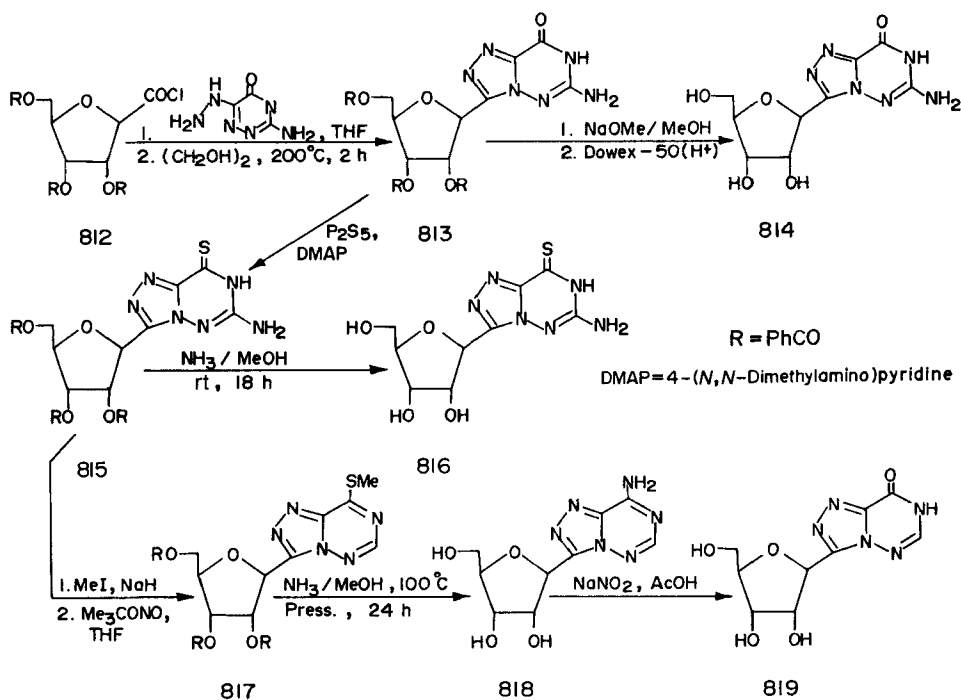
SCHEME 213

5-one followed by removal of the protective groups. Compounds **816**, **818**, and **819**, belonging to this class and related to thioguanosine, adenosine and formycin, and inosine and formycin B, respectively, were prepared according to the nucleoside–nucleoside transformation approaches shown in Scheme 214 (86JMC2231). Only C-nucleoside **818** possessed pronounced antitumor activity toward L-1210, WIL2, and CCRF-CEM cell lines in culture (86JMC2231).

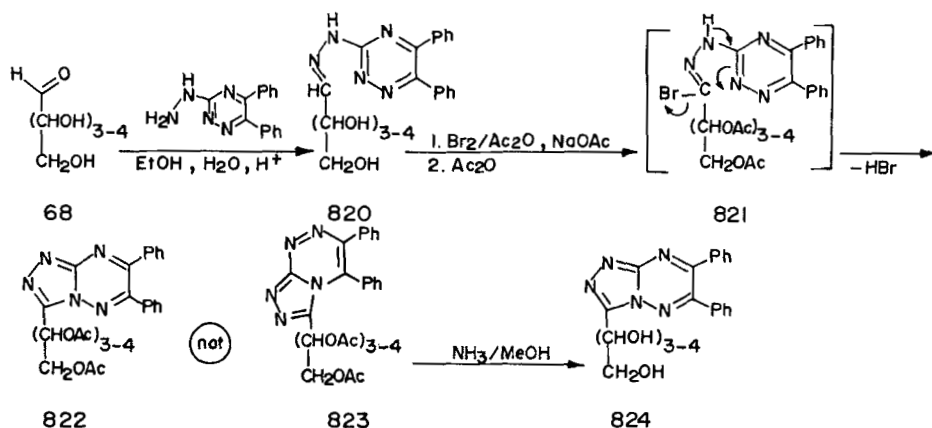
F. 1,2,4-Triazolo[4,3-*b*]1,2,4-triazine ACYCLO C-NUCLEOSIDES

1. 1,2,4-Triazolo[4,3-*b*]1,2,4-triazin-3-yl Acyclo C-Nucleosides

Oxidative cyclization of (5,6-diphenyl-1,2,4-triazin-3-yl)hydrazones of aldose monosaccharides (**820**) and concurrent acetylation of the alditolyl chain hydroxyls provided the corresponding *O*-acetylated 3-(alditol-1-yl)-6,7-diphenyl-1,2,4-triazolo[4,3-*b*]1,2,4-triazines **822** and not the alternative structure **823**. De-*O*-acetylation of **822** gave **824** (96PHA707) (Scheme 215).



SCHEME 214



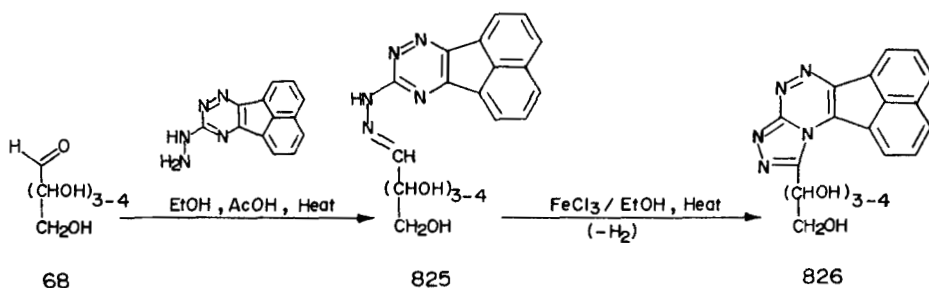
SCHEME 215

The acyclo *C*-nucleoside **824** having an *L*-arabino-tetritolyl chain possessed antibacterial activity against *Bacillus subtilis* (97UP2).

G. 1,2,4-TRIAZOLO[3,4-*c*]1,2,4-TRIAZINE ACYCLO *C*-NUCLEOSIDES

1. 1,2,4-Triazolo[3,4-*c*]1,2,4-triazin-1-yl Acyclo *C*-Nucleosides

Dehydrogenative cyclization of aldose {acenaphtho[1,2-*e*]1,2,4-triazin-3-yl}hydrazones (**825**) with ethanolic iron(III) chloride provided 1-(alditol-1-yl)acenaphtho[1,2-*e*]1,2,4-triazolo[3,4-*c*]1,2,4-triazines (**826**). That cyclization occurred at N4 rather than at N2 of the 1,2,4-triazine ring was based on comparison with similar noncarbohydrate products (94BCJ149) (Scheme 216).



SCHEME 216

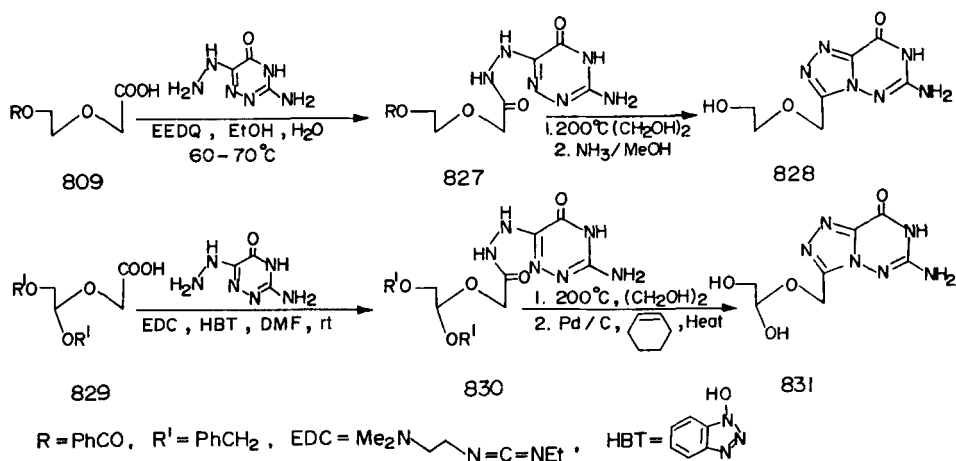
H. 1,2,4-TRIAZOLO[3,4-*f*]1,2,4-TRIAZINE ACYCLO C-NUCLEOSIDES1. 1,2,4-Triazolo[3,4-*f*]1,2,4-triazin-3-yl Acyclo C-Nucleosides

Coupling of [2-(benzoyloxy)ethoxy]acetic acid (**809**) or [2-(1,3-dibenzyloxy)propoxy]acetic acid **829** with 3-amino-6-hydrazino-1,2,4-triazin-5-one gave the two amides **827** and **830**, respectively. Thermal cyclodehydration of **827** and **830** and subsequent deprotection gave the two truncated-sugar acyclo C-nucleosides **828** (84JHC697) and **831** (95MI6) (Scheme 217).

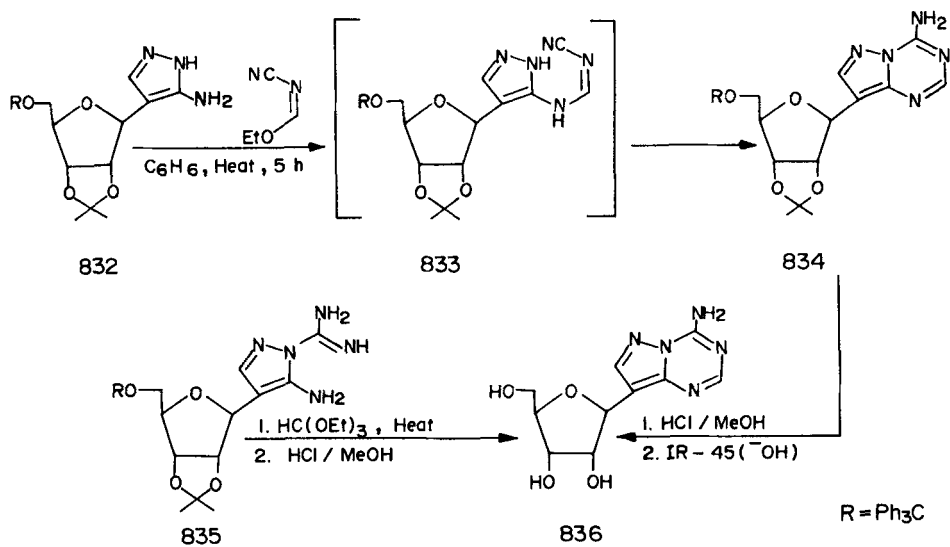
XVI. Condensed 1,3,5-Triazine C-Nucleosides

A. PYRAZOLO[1,5-*a*]1,3,5-TRIAZINE C-NUCLEOSIDES1. *Pyrazolo*[1,5-*a*]1,3,5-triazin-8-yl C-Nucleosides

The most commonly used strategy for the synthesis of this class of C-nucleosides was the annulation of the 1,3,5-triazine ring onto suitably substituted pyrazol-4-yl C-nucleosides. Thus, the C-nucleosides **836**, related to adenosine and formycin, was prepared by reacting the 3-aminopyrazol-4-yl C-nucleoside **832** with ethoxy *N*-cyanoformimidate (76JHC1305; 96MI2) or by reacting the 3-amino-2-carbamimidoylpyrazol-4-yl C-nucleoside **835** with triethyl orthoformate [84H(22)345] (Scheme 218).



SCHEME 217



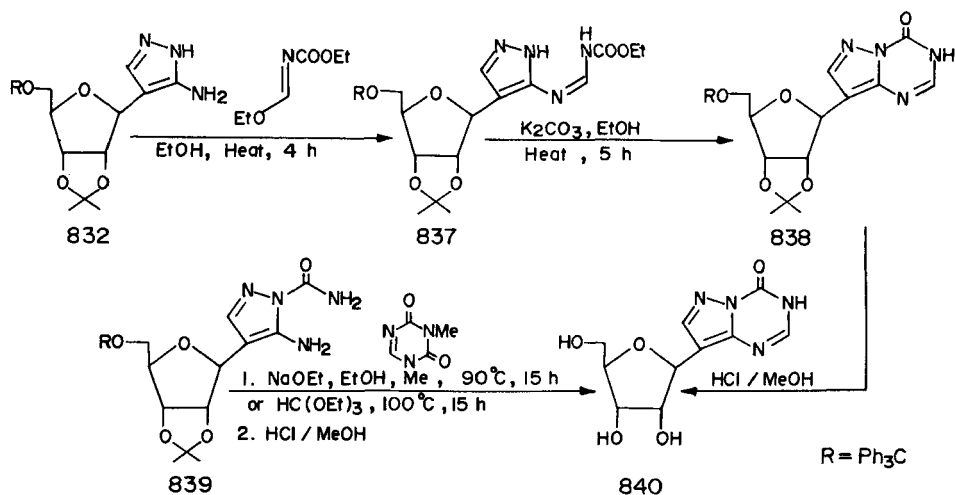
SCHEME 218

Prepared by similar reactions was the 8-(β-D-ribofuranosyl)pyrazolo[1,5-*a*]1,3,5-triazin-4-one (**840**) related to inosine and formycin. In one route **832** reacted with *N*-ethoxycarbonylformimidate (76JHC1305), and in the other the 3-amino-2-carbamoylpyrazol-4-yl *C*-nucleoside **839** reacted with triethyl orthoformate (80JHC1435) or 1,3-dimethyl-1,3,5-triazine-2,6-dione in the presence of sodium ethoxide (86JHC349) (Scheme 219).

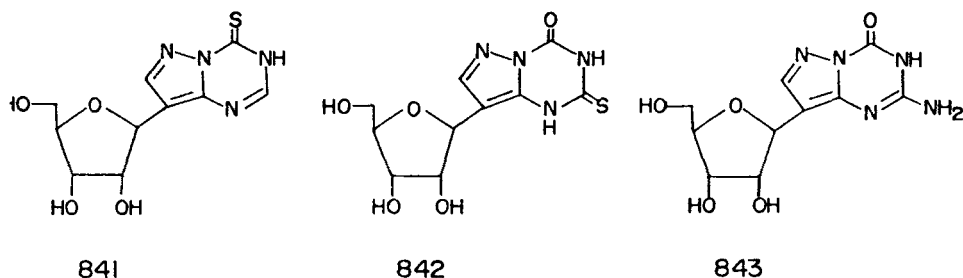
4-Thioxo- (**841**) (79JOC4547; 84JHC389), 4-oxo-2-thioxo- (**842**) (76-JHC175), and 2-amino-4-oxopyrazolo[1,5-*a*]1,3,5-triazin-3-yl *C*-nucleosides (**843**) (79JOC4547) were also prepared by very similar reactions.

C-Nucleosides **836**, **840**, and **841** revealed potent antileukemic properties toward L-1210 and P815 cell lines *in vitro* (76JHC1305; 78MI4; 79JOC4547).

Synthesis of the 2'-deoxy-β-D-ribofuranosylpyrazolo[1,5-*a*]1,3,5-triazine **847** has been achieved by C—C bond formation between the sugar and heterocycle subunits. Palladium-mediated coupling of the 3-*O*-silylated furanoid glycal (1,2-unsaturated sugar) **454** with 8-iodo-4-(tetrahydropyran-2-yloxy)pyrazolo[1,5-*a*]1,3,5-triazine in the presence of triphenylarsine gave **844**. De-*O*-silylation of **844** and stereospecific reduction of the keto group of **846** afforded **847** (95MI3) (Scheme 220).



SCHEME 219



B. PYRAZOLO[1,5-f]1,3,5-TRIAZINE ACYCLO C-NUCLEOSIDES

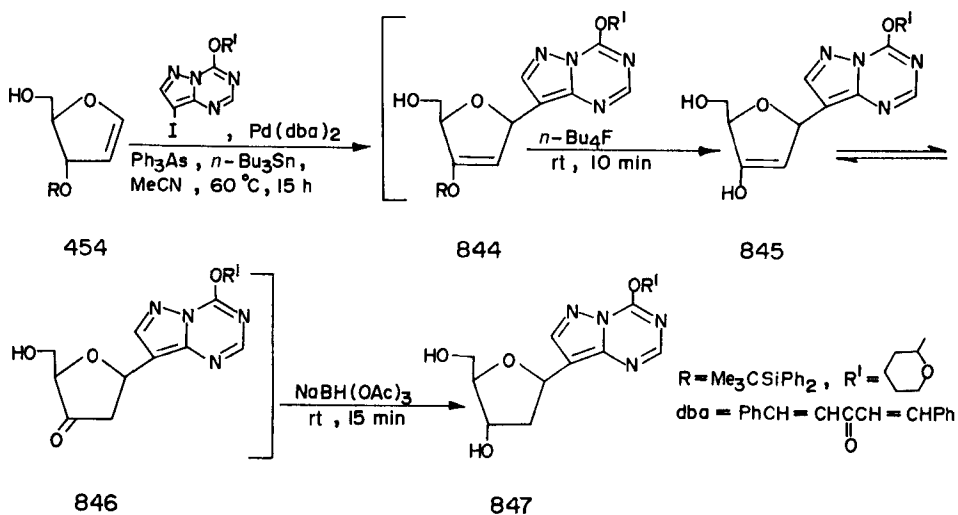
1. Pyrazolo[1,5-f]1,3,5-triazin-8-yl Acyclo C-Nucleosides

The acyclo C-nucleosides **850–852** were synthesized by reactions that involved the annulation of their 1,3,5-triazine rings onto the pyrazol-4-yl acyclo C-nucleosides **848** and **849**, as shown in Scheme 221 (88JOC2413).

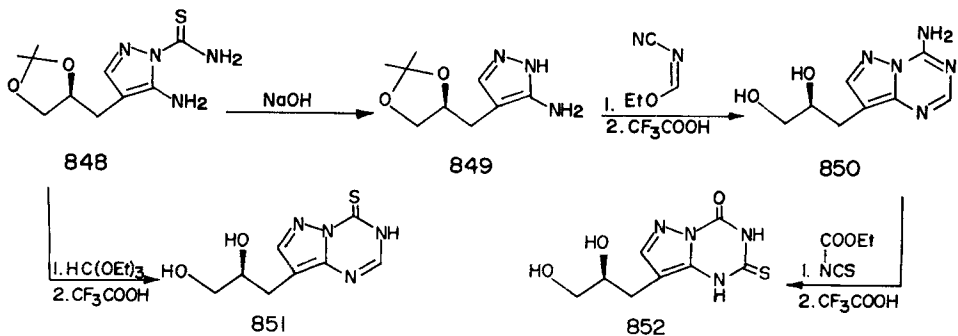
C. IMIDAZO[1,5-a]1,3,5-TRIAZINE ACYCLO C-NUCLEOSIDES

1. Imidazo[1,5-a]1,3,5-triazin-8-yl Acyclo C-Nucleosides

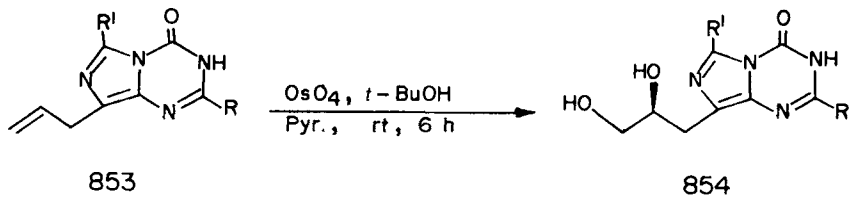
cis-1,2-Hydroxylation of the allyl double bond of 8-allylimidazo[1,5-a]1,3,5-triazin-4-ones (**853**) with osmium tetroxide gave the corresponding acyclo C-nucleosides of this type **854**, which did not appreciably inhibit viruses or tumor cells (87MI5) (Scheme 222).



SCHEME 220



SCHEME 221



SCHEME 222

XVII. Condensed 1,4-Diazepine C-Nucleosides**A. BENZO[*b*]THIAZOLO[3,2-*d*]1,4-DIAZEPINE
ACYCLO C-NUCLEOSIDES****1. Benzo[*b*]thiazolo[3,2-*d*]1,4-diazepin-1-yl Acyclo C-Nucleosides**

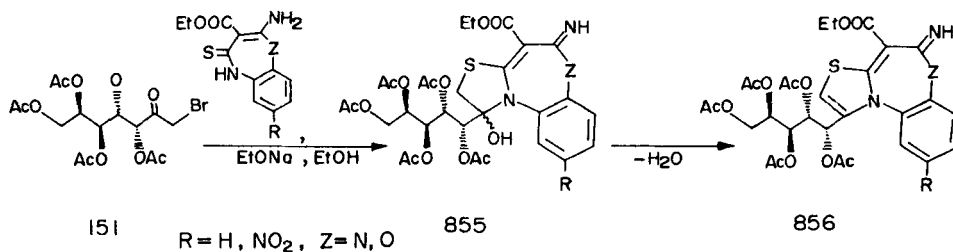
Cyclocondensation of 1-bromo-1-deoxy-D-*galacto*-heptulose pentaacetate (**151**) with 2-amino-4-thioxo-4,5-dihydrobenzo[*b*]1,4-diazepine-3-carboxylic acid ester provided **856** ($Z = N$) [85GEP(D)216938; 86PHA548] (Scheme 223).

XVIII. Condensed 1,4-Oxazepine C-Nucleosides**A. BENZO[*b*]THIAZOLO[3,2-*d*]1,4-OXAZEPINE
ACYCLO C-NUCLEOSIDES****1. Benzo[*b*]thiazolo[3,2-*d*]1,4-oxazepin-1-yl Acyclo C-Nucleosides**

The acyclo C-nucleosides **856** ($Z = O$) were prepared from **151** and 2-amino-4-thioxo-4,5-dihydro[*b*]1,4-oxazepine-3-carboxylic acid ester [85GEP(D)216938; 86PHA548] (Scheme 223).

XIX. Condensed 1,5-Diazepine C-Nucleosides**A. BENZO[*f*]1,5-DIAZEPINE HOMO C-NUCLEOSIDES****1. Benzo[*f*]1,5-diazepin-4-yl Homo C-Nucleosides**

Mixtures of 7- and 8-substituted benzo[*f*]-2-oxo-1,5-diazepin-4-yl homo C-nucleosides **857** were obtained by the reaction of 5-hydroxy-5-β-D-ribofuranosylfuran-2-one (**247**) with 4-substituted-1,2-diaminobenzenes



SCHEME 223

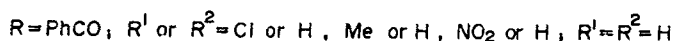
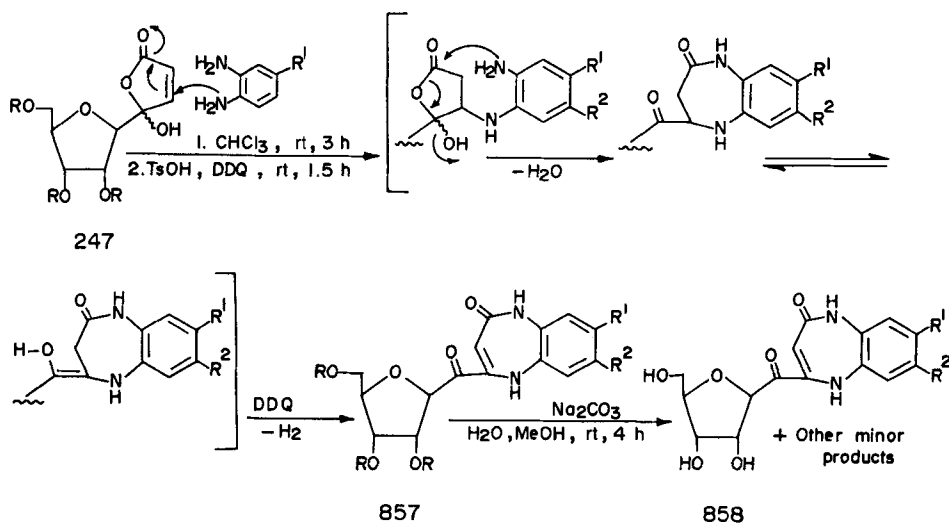
in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). De-*O*-benzylation of **857** gave the unprotected *C*-nucleosides **858** [91H-(32)1955; 92H(34)955] (Scheme 224).

XX. Condensed 1,5-Thiazepine *C*-Nucleosides

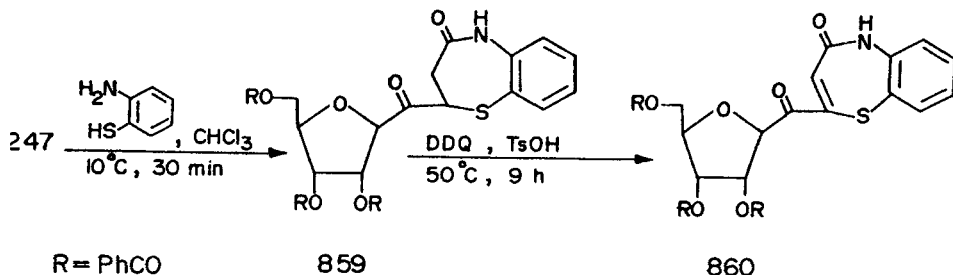
A. BENZO[*f*]1,5-THIAZEPINE HOMO *C*-NUCLEOSIDES

1. Benzo[*f*]1,5-thiazepin-2-yl Homo *C*-Nucleosides

Reaction of **247** with 2-aminothiophenol under the same conditions that were applied for the preparation of **857** gave **860** [92H(34)2131] (Scheme 225). Attempted de-*O*-benzylation of **860** resulted in the formation of the unsaturated *C*-nucleosides having a C=C between C1' and C2' [92H(34)2131].



SCHEME 224



SCHEME 225

XXI. Condensed 1,3,5-Triazepine C-Nucleosides

A. BENZO[*f*]1,3,5-TRIAZEPINE ACYCLO C-NUCLEOSIDES

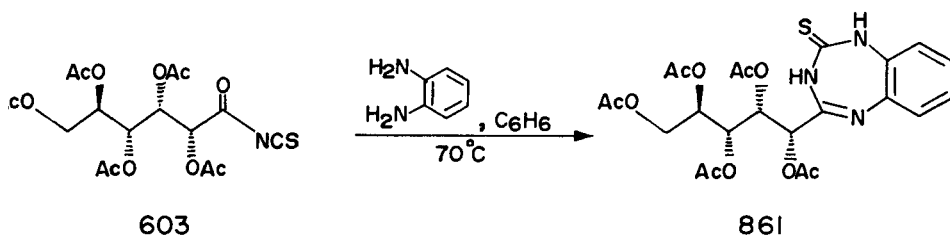
1. Benzo[*ff*]1,3,5-triazepin-4-yl Acyclo C-Nucleosides

2,3,4,5,6-Tetra-*O*-acetyl-D-gluconoyl isothiocyanate (**603**) cyclocondensed with 1,2-diaminobenzene to give the acyclo C-nucleoside **861** (Scheme 226). It possessed antibacterial, antiviral, and psychotropic activities [75MI6; 76JAP(K)76/39685; 81CPB1832].

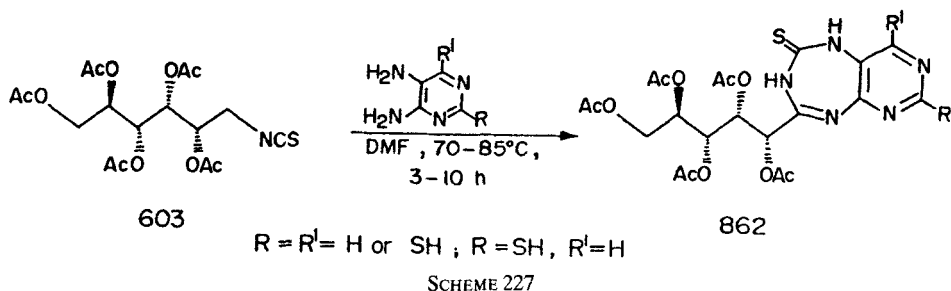
B. PYRIMIDO[4,5-*f*]1,3,5-TRIAZEPINE ACYCLO C-NUCLEOSIDES

1. Pyrimido[4,5-*ff*]1,3,5-triazepin-4-yl Acyclo C-Nucleosides

Utilization of 4,5-diaminopyrimidines in place of 1,2-diaminobenzene in the aforementioned cyclocondensation reaction produced the acyclo C-nucleosides of this class **862** (Scheme 227) [76JAP(K)76/39685; 76MI6, 81CPB1832].



SCHEME 226



XXII. Conclusion

The term “C-nucleoside” was only coined after isolation and characterization of the first member of this class: pseudouridine, in 1975 [97ACH(ip)]. Before that, alditolyl derivatives of some heterocycles (acyclo C-nucleosides) were known both as natural products (alditolyl pteridines or biopterins) as well as products of syntheses (e.g., alditolyl derivatives of imidazoles, benzimidazoles, thiazoles, benzothiazoles, 1,2,3-triazoles, quinoxalines, and flavazoles) and were classified as “carbohydrate derivatives of heterocyclic compounds.” After isolation of pseudouridine, other naturally occurring members were successively isolated, characterized, and synthesized. It is worth mentioning that synthesis preceded isolation in two cases: 9-deazaadenosine and pyrrolosine. Comparison with the synthetic compounds facilitated structure elucidation in one case (9-deazaadenosine) and structure reassignment in the other (pyrrolosine).

C-Nucleosides are able to biologically mimic N-nucleosides without undergoing the same metabolic fate. As a result, they exhibit a wide spectrum of biological activities. Their promise in potential utilization as medicinal products stimulated extensive efforts to synthesize C-nucleosides as well as their analogs (homo, carbocyclic, reverse, and acyclo). Such efforts undoubtedly have been encouraged by the persistent search for drugs that are able to inhibit human immunodeficiency viruses (HIV), the causative agent of AIDS. A reasonably large number of C-nucleosides carrying various five- and six-membered nitrogen-containing heterocycles were prepared. Less attention, however, was directed toward the synthesis of C-nucleosides of seven-membered nitrogen-containing heterocycles, to which many of the behavior-controlling drugs belong. Research along this line may lead to products with better properties to overcome the blood–brain barrier and/or the blood–cerebrospinal fluid barrier (93MI4). In short, the synthesis of new C-nucleosides and C-nucleoside analogs is highly desirable and awaits accomplishment.

ACKNOWLEDGMENT

The author is indebted to Professor Zaki M. El Shafei for his invaluable suggestions and proofreading of the manuscript. MAES would like to dedicate the two parts of this review to Professor Roger W. Jeanloz, with whom he started his professional career (1970–1972 and 1974–1976) at Harvard Medical School, on the occasion of his 75th birthday.

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